(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 August 2005 (25.08.2005)

PCT

(10) International Publication Number
WO 2005/077042 A2

(51) International Patent Classification: Not classified

(21) International Application Number: PCT/US2005/004041

(22) International Filing Date: 9 February 2005 (09.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/542,274	9 February 2004 (09.02.2004)	US
60/549,901	5 March 2004 (05.03.2004)	US
60/556,906	29 March 2004 (29.03.2004)	US
60/636,603	17 December 2004 (17.12.2004)	US

(71) Applicant *(for all designated States except US)*: **HUMAN GENOME SCIENCES, INC.** [US/US]; 14200 Shady Grove Road, Rockville, Maryland 20850 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ROSEN, Craig, A.** [US/US]; 22400 Rolling Hill Lane, Laytonsville, Maryland 20882 (US). **HASELTINE, William, A.** [US/US]; 3053 P Street, N.W., Washington, D 20007 (US). **MOORE, Paul, A.** [GB/US]; 7013 Old Gate Road, North Bethesda, Maryland 20852 (US). **BOCK, Jason, B.** [US/US]; 14200 Secluded Lane, North Potomac, Maryland 20878 (US). **BELL, Adam** [US/US]; 13312 Burnt Woods Place, Germantown, Maryland 20874 (US). **SHI, Yanggu** [US/US]; 710 Suffield Drive, Gaithersburg, Maryland 20878 (US). **LAFLEUR, David** [US/US]; 3142 Quesada Street, N.W., Washington, D 20015 (US).

(74) Agents: **WALES, Michele, M.** et al.; 14200 Shady Grove Road, Rockville, MD 20850 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,

[Continued on next page]

(54) Title: ALBUMIN FUSION PROTEINS

```
  1 GAT GCA CAC AAG AGT GAG GTT GCT CAT CGG TTT AAA GAT TTG GGA GAA GAA AAT TTC AAA 60
  1 D   A   H   K   S   E   V   A   H   R   F   K   D   L   G   E   E   N   F   K   20

 61 GCC TTG GTG TTG ATT GCC TTT GCT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120
 21 A   L   V   L   I   A   F   A   Q   Y   L   Q   Q   C   P   F   E   D   H   V   40

121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GCA AAA ACA TGT GTT GCT GAT GAG TCA GCT GAA 180
 41 K   L   V   N   E   V   T   E   F   A   K   T   C   V   A   D   E   S   A   E   60

181 AAT TGT GAC AAA TCA CTT CAT ACC CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 240
 61 N   C   D   K   S   L   H   T   L   F   G   D   K   L   C   T   V   A   T   L   80

241 CGT GAA ACC TAT GGT GAA ATG GCT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300
 81 R   E   T   Y   G   E   M   A   D   C   C   A   K   Q   E   P   E   R   N   E   100

301 TGC TTC TTG CAA CAC AAA GAT GAC AAC CCA AAC CTC CCC CGA TTG GTG AGA CCA GAG GTT 360
101 C   F   L   Q   H   K   D   D   N   P   N   L   P   R   L   V   R   P   E   V   120

361 GAT GTG ATG TGC ACT GCT TTT CAT GAC AAT GAA GAG ACA TTT TTG AAA AAA TAC TTA TAT 420
121 D   V   M   C   T   A   F   H   D   N   E   E   T   F   L   K   K   Y   L   Y   140

421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTC TTT GCT AAA AGG 480
141 E   I   A   R   R   H   P   Y   F   Y   A   P   E   L   L   F   F   A   K   R   160
```

(57) Abstract: The present invention encompasses albumin fusion proteins. Nucleic acid molecules encoding the albumin fusion proteins of the invention are also encompassed by the invention, as are vectors containing these nucleic acids, host cells transformed with these nucleic acids vectors, and methods of making the albumin fusion proteins of the invention and using these nucleic acids, vectors, and/or host cells. Additionally the present invention encompasses pharmaceutical compositions comprising albumin fusion proteins and methods of treating, preventing, or ameliorating diseases, disorders or conditions using albumin fusion proteins of the invention.

WO 2005/077042 A2

TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Albumin Fusion Proteins

REFERENCE TO SEQUENCE LISTING ON COMPACT DISC

[0001] This application refers to a "Sequence Listing" listed below, which is provided as an electronic document on three identical compact discs (CD-R), labeled "Copy 1," "Copy 2," and "Copy 3." These compact discs each contain the file "PF612PCT SL.txt" (929,048 bytes, created on February 7, 2005), which is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The invention relates generally to Therapeutic proteins (including, but not limited to, at least one polypeptide, antibody, peptide, or fragment and variant thereof) fused to albumin or fragments or variants of albumin. The invention encompasses polynucleotides encoding therapeutic albumin fusion proteins, therapeutic albumin fusion proteins, compositions, pharmaceutical compositions, formulations and kits. Host cells transformed with the polynucleotides encoding therapeutic albumin fusion proteins are also encompassed by the invention, as are methods of making the albumin fusion proteins of the invention using these polynucleotides, and/or host cells.

[0003] Human serum albumin (HSA, or HA), a protein of 585 amino acids in its mature form (as shown in Figure 1 (SEQ ID NO:1)), is responsible for a significant proportion of the osmotic pressure of serum and also functions as a carrier of endogenous and exogenous ligands. At present, HA for clinical use is produced by extraction from human blood. The production of recombinant HA (rHA) in microorganisms has been disclosed in EP 330 451 and EP 361 991.

[0004] Therapeutic proteins in their native state or when recombinantly produced, such as interferons and growth hormones, are typically labile molecules exhibiting short shelf-lives, particularly when formulated in aqueous solutions. The instability in these molecules when formulated for administration dictates that many of the molecules must be lyophilized and refrigerated at all times during storage, thereby rendering the molecules difficult to transport and/or store. Storage problems are particularly acute when pharmaceutical formulations must be stored and dispensed outside of the hospital environment.

[0005] Few practical solutions to the storage problems of labile protein molecules have been proposed. Accordingly, there is a need for stabilized, long lasting formulations of proteinaceous therapeutic molecules that are easily dispensed, preferably with a simple formulation requiring minimal post-storage manipulation.

[0006] Upon *in vivo* administration, therapeutic proteins in their native state or when recombinantly produced, such as interferons and growth hormones, exhibit a short plasma stability due to rapid clearance from the bloodstream. Accordingly, the therapeutic effects provided by these proteins are also short-lived. Thus, in order to sustain their desired therapeutic effect *in vivo*, the rapid clearance of these proteins from the blood dictates that the therapeutic molecules must be administered more frequently or at a higher dose. However, increasing the dosing schedule for administration of the therapeutic protein often results in an increase in injection site reactions, side-effects, and toxicity in the patient. Similarly, administration of the therapeutic protein at a higher dose also commonly results in an increase in toxicity and side-effects in the patient.

[0007] The few practical solutions to increasing plasma stability of therapeutic molecules that have been proposed, including chemical conjugation, have provided limited benefit to the patient. Generally, in most cases, these chemically modified therapeutic molecules are still administered on a frequent dosing schedule, retaining significant injection site reactions, side-effects, and toxicity in patients. Accordingly, there is a need for an stabilized form of therapeutic molecules that retains a higher plasma stability in vivo than the native or recombinantly produced therapeutic alone and can be administered less frequently, thereby decreasing potential side-effects to the patient.

SUMMARY OF THE INVENTION

[0008] The present invention encompasses albumin fusion proteins comprising a Therapeutic protein (e.g., a polypeptide, antibody, or peptide, or fragment or variant thereof) fused to albumin or a fragment (portion) or variant of albumin. The present invention also encompasses polynucleotides comprising, or alternatively consisting of, nucleic acid molecules encoding a Therapeutic protein (e.g., a polypeptide, antibody, or peptide, or fragment or variant thereof) fused to albumin or a fragment (portion) or variant of albumin. The present invention also encompasses polynucleotides, comprising, or alternatively consisting of, nucleic acid molecules encoding proteins comprising a Therapeutic protein (e.g., a polypeptide, antibody, or peptide, or fragment or variant thereof) fused to albumin or a fragment (portion) or variant of albumin, that is sufficient to prolong the shelf life of the Therapeutic protein, to increase the plasma stability of the Therapeutic protein compared to its unfused state, and/or stabilize the Therapeutic protein and/or its activity in solution (or in a pharmaceutical composition) *in vitro* and/or *in vivo*. Albumin fusion proteins encoded by a polynucleotide of the invention are also encompassed by the invention, as are host cells transformed with polynucleotides of the invention, and methods of making the albumin fusion proteins of the invention and using these polynucleotides of the invention, and/or host cells.

[0009] In a preferred aspect of the invention, albumin fusion proteins include, but are not limited to, those described in Table 2 and the polynucleotides encoding such proteins.

[0010] The invention also encompasses pharmaceutical formulations comprising an albumin fusion protein of the invention and a

pharmaceutically acceptable diluent or carrier. Such formulations may be in a kit or container. Such kit or container may be packaged with instructions pertaining to the extended shelf life of the Therapeutic protein. Such formulations may be used in methods of treating, preventing, ameliorating or diagnosing a disease or disease symptom in a patient, preferably a mammal, most preferably a human, comprising the step of administering the pharmaceutical formulation to the patient.

[0011] In other embodiments, the present invention encompasses methods of preventing, treating, or ameliorating a disease or disorder. In preferred embodiments, the present invention encompasses a method of treating a disease or disorder listed in the "Preferred Indication: Y" column of Table 1 comprising administering to a patient in which such treatment, prevention or amelioration is desired an albumin fusion protein of the invention that comprises a Therapeutic protein or portion corresponding to a Therapeutic protein (or fragment or variant thereof) disclosed in the "Therapeutic Protein: X" column of Table 1 (in the same row as the disease or disorder to be treated as listed in the "Preferred Indication: Y" column of Table 1) in an amount effective to treat, prevent or ameliorate the disease or disorder.

[0012] In one embodiment, an albumin fusion protein described in Table 1 or 2 has extended shelf life.

[0013] In a second embodiment, an albumin fusion protein described in Table 1 or 2 is more stable than the corresponding unfused Therapeutic molecule described in Table 1.

[0014] The present invention further includes transgenic organisms modified to contain the nucleic acid molecules of the invention (including, but not limited to, the polynucleotides described in Tables 1 and 2), preferably modified to express an albumin fusion protein of the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0015] Figure 1A-D shows the amino acid sequence of the mature form of human albumin (SEQ ID NO:1) and a polynucleotide encoding it (SEQ ID NO:2). Nucleotides 1 to 1755 of SEQ ID NO:2 encode the mature form of human albumin (SEQ ID NO:1).

[0016] Figure 2 shows the restriction map of the pPPC0005 cloning vector ATCC deposit PTA-3278.

[0017] Figure 3 shows the restriction map of the pSAC35 yeast *S. cerevisiae* expression vector (Sleep *et al.*, BioTechnology 8:42 (1990)).

[0018] Figure 4 shows the effect of various dilutions of IFNb albumin fusion proteins encoded by DNA comprised in CID 2011 and 2053 on SEAP activity in the ISRE-SEAP/293F reporter cells (see Example 76). Proteins were serially diluted from 5e-7 to 1e-14 g/ml in DMEM/10% FBS and used to treat ISRE-SEAP/293F reporter cells. After 24 hours supernatants were removed from reporter cells and assayed for SEAP activity. IFNb albumin fusion protein was purified from three stable clones: 293F/#2011, CHO/#2011 and NSO/#2053. Mammalian derived IFNb, Avonex, came from Biogen and was reported to have a specific activity of 2.0e5 IU/ug.

[0019] Figure 5 compares the anti-proliferative activity of IFN albumin fusion protein encoded by CID 3165 (CID 3165 protein) and recombinant IFNa (rIFNa) on Hs294T melanoma cells. The cells were cultured with varying concentrations of either CID 3165 protein or rIFNa and proliferation was measured by BrdU incorporation after 3 days of culture. CID 3165 protein caused measurable inhibition of cell proliferation at concentrations above 10 ng/ml with 50% inhibition achieved at approximately 200 ng/ml. (■) = CID 3165 protein, (◆) = rIFNa.

[0020] Figure 6 shows the effect of various dilutions of IFNa albumin fusion proteins on SEAP activity in the ISRE-SEAP/293F reporter cells. One preparation of IFNa fused upstream of albumin (◆) was tested, as well as two different preparations of IFNa fused downstream of albumin (●) and (■).

[0021] Figure 7 shows the effect of time and dose of IFNa albumin fusion protein encoded by DNA comprised in construct 2249 (CID 2249 protein) on the mRNA level of OAS (p41) in treated monkeys (see Example 78). Per time point: first bar = Vehicle control, 2nd bar = 30 ug/kg CID 2249 protein day 1 iv, third bar = 30 ug/kg CID 2249 protein day 1 sc, 4th bar = 300 ug/kg CID 2249 protein day 1 sc, 5th bar = 40 ug/kg recombinant IFNa day 1, 3 and 5 sc.

[0022] Figure 8 shows the dose-response relationship of BNP albumin fusion proteins encoded by DNA comprised in constructs CID 3691 and 3618 (CID 3691 and 3618 protein) on activating cGMP formation in NPR-A/293F reporter cells (see Examples 80 and 81). Both recombinant BNP (■), as well as, two different preparations of BNP fused upstream of albumin (□) and (●) were tested.

[0023] Figure 9 shows the effect of BNP albumin fusion protein on mean arterial pressure in spontaneously hypertensive rats (see Example 80). Vehicle (□), recombinant BNP protein (●), or BNP albumin fusion protein (O) were delivered via tail vein injection. Systolic and diastolic blood pressures were recorded by cuff-tail method

[0024] Figure 10 shows the plasma cGMP levels in eleven- to 12-week-old male C57/BL6 mice after intravenous injection of recombinant BNP protein (●) or BNP albumin fusion protein (O (see Example 80). cGMP levels were determined from plasma prepared from tail bleeds collected at several time points after intravenous injection.

[0025] Figure 11 shows the blood glucose levels in fasted ~8-week old diabetic db/db mice 24 hours after single administration of tandem GLP-1(7-36A8G)2x-HSA fusion (CID 3610) (◇), monomer GLP-1(7-36A8G)-HSA fusion (△), or HSA alone (●). Blood glucose levels were measured by an oral glucose tolerance test. Tandem GLP-1(7-36A8G)2x-HSA fusion (CID 3610) (◇) had an unexpected more potent glucose-normalizing activity than the monomer GLP-1(7-36A8G)-HSA fusion (△) 24 hours after a single administration in fasted ~8 week old diabetic db/db mice.

DETAILED DESCRIPTION

Definitions

[0026] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[0027] As used herein, "polynucleotide" refers to a nucleic acid molecule having a nucleotide sequence encoding a fusion protein comprising, or alternatively consisting of, at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one Therapeutic protein X (or fragment or variant thereof); a nucleic acid molecule having a nucleotide sequence encoding a fusion protein comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NO:Y (as described in column 6 of Table 2) or a fragment or variant thereof; a nucleic acid molecule having a nucleotide sequence comprising or alternatively consisting of the sequence shown in SEQ ID NO:X; a nucleic acid molecule having a nucleotide sequence encoding a fusion protein comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NO:Z; a nucleic acid molecule having a nucleotide sequence encoding an albumin fusion protein of the invention generated as described in Table 2 or in the Examples; a nucleic acid molecule having a nucleotide sequence encoding a Therapeutic albumin fusion protein of the invention, a nucleic acid molecule having a nucleotide sequence contained in an albumin fusion construct described in Table 2, or a nucleic acid molecule having a nucleotide sequence contained in an albumin fusion construct deposited with the ATCC (as described in Table 3).

[0028] As used herein, "albumin fusion construct" refers to a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof); a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof) generated as described in Table 2 or in the Examples; or a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof), further comprising, for example, one or more of the following elements: (1) a functional self-replicating vector (including but not limited to, a shuttle vector, an expression vector, an integration vector, and/or a replication system), (2) a region for initiation of transcription (e.g., a promoter region, such as for example, a regulatable or inducible promoter, a constitutive promoter), (3) a region for termination of transcription, (4) a leader sequence, and (5) a selectable marker. The polynucleotide encoding the Therapeutic protein and albumin protein, once part of the albumin fusion construct, may each be referred to as a "portion," "region" or "moiety" of the albumin fusion construct.

[0029] The present invention relates generally to polynucleotides encoding albumin fusion proteins; albumin fusion proteins; and methods of treating, preventing, or ameliorating diseases or disorders using albumin fusion proteins or polynucleotides encoding albumin fusion proteins. As used herein, "albumin fusion protein" refers to a protein formed by the fusion of at least one molecule of albumin (or a fragment or variant thereof) to at least one molecule of a Therapeutic protein (or fragment or variant thereof). An albumin fusion protein of the invention comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another by genetic fusion (i.e., the albumin fusion protein is generated by translation of a nucleic acid in which a polynucleotide encoding all or a portion of a Therapeutic protein is joined in-frame with a polynucleotide encoding all or a portion of albumin). The Therapeutic protein and albumin protein, once part of the albumin fusion protein, may each be referred to as a "portion", "region" or "moiety" of the albumin fusion protein (e.g., a "Therapeutic protein portion" or an "albumin protein portion"). In a highly preferred embodiment, an albumin fusion protein of the invention comprises at least one molecule of a Therapeutic protein X or fragment or variant of thereof (including, but not limited to a mature form of the Therapeutic protein X) and at least one molecule of albumin or fragment or variant thereof (including but not limited to a mature form of albumin).

[0030] In a further preferred embodiment, an albumin fusion protein of the invention is processed by a host cell and secreted into the surrounding culture medium. Processing of the nascent albumin fusion protein that occurs in the secretory pathways of the host used for expression may include, but is not limited to signal peptide cleavage; formation of disulfide bonds; proper folding; addition and processing of carbohydrates (such as for example, N- and O- linked glycosylation); specific proteolytic cleavages; and assembly into multimeric proteins. An albumin fusion protein of the invention is preferably in the processed form. In a most preferred embodiment, the "processed form of an albumin fusion protein" refers to an albumin fusion protein product which has undergone N- terminal signal peptide cleavage, herein also referred to as a "mature albumin fusion protein".

[0031] In several instances, a representative clone containing an albumin fusion construct of the invention was deposited with the American Type Culture Collection (herein referred to as "ATCC®"). Furthermore, it is possible to retrieve a given albumin fusion construct from the deposit by techniques known in the art and described elsewhere herein. The ATCC® is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC® deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0032] In one embodiment, the invention provides a polynucleotide encoding an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a serum albumin protein. In a further embodiment, the invention provides an albumin fusion protein comprising, or

alternatively consisting of, a Therapeutic protein and a serum albumin protein. In a preferred embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a serum albumin protein encoded by a polynucleotide described in Table 2. In a further preferred embodiment, the invention provides a polynucleotide encoding an albumin fusion protein whose sequence is shown as SEQ ID NO:Y in Table 2. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment of a Therapeutic protein and a serum albumin protein. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active variant of a Therapeutic protein and a serum albumin protein. In preferred embodiments, the serum albumin protein component of the albumin fusion protein is the mature portion of serum albumin. The invention further encompasses polynucleotides encoding these albumin fusion proteins.

[0033] In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein, and a biologically active and/or therapeutically active fragment of serum albumin. In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a biologically active and/or therapeutically active variant of serum albumin. In preferred embodiments, the Therapeutic protein portion of the albumin fusion protein is the mature portion of the Therapeutic protein. In a further preferred embodiment, the Therapeutic protein portion of the albumin fusion protein is the extracellular soluble domain of the Therapeutic protein. In an alternative embodiment, the Therapeutic protein portion of the albumin fusion protein is the active form of the Therapeutic protein. The invention further encompasses polynucleotides encoding these albumin fusion proteins.

[0034] In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment or variant of a Therapeutic protein and a biologically active and/or therapeutically active fragment or variant of serum albumin. In preferred embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, the mature portion of a Therapeutic protein and the mature portion of serum albumin. The invention further encompasses polynucleotides encoding these albumin fusion proteins.

<u>Therapeutic proteins</u>

[0035] As stated above, a polynucleotide of the invention encodes a protein comprising or alternatively consisting of, at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion.

[0036] An additional embodiment includes a polynucleotide encoding a protein comprising or alternatively consisting of at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are linked with one another by chemical conjugation.

[0037] As used herein, "Therapeutic protein" refers to proteins, polypeptides, antibodies, peptides or fragments or variants thereof, having one or more therapeutic and/or biological activities. Therapeutic proteins encompassed by the invention include but are not limited to, proteins, polypeptides, peptides, antibodies, and biologics. (The terms peptides, proteins, and polypeptides are used interchangeably herein.) It is specifically contemplated that the term "Therapeutic protein" encompasses antibodies and fragments and variants thereof. Thus a protein of the invention may contain at least a fragment or variant of a Therapeutic protein, and/or at least a fragment or variant of an antibody. Additionally, the term "Therapeutic protein" may refer to the endogenous or naturally occurring correlate of a Therapeutic protein.

[0038] By a polypeptide displaying a "therapeutic activity" or a protein that is "therapeutically active" is meant a polypeptide that possesses one or more known biological and/or therapeutic activities associated with a therapeutic protein such as one or more of the Therapeutic proteins described herein or otherwise known in the art. As a non-limiting example, a "Therapeutic protein" is a protein that is useful to treat, prevent or ameliorate a disease, condition or disorder. As a non-limiting example, a "Therapeutic protein" may be one that binds specifically to a particular cell type (normal (e.g., lymphocytes) or abnormal e.g., (cancer cells)) and therefore may be used to target a compound (drug, or cytotoxic agent) to that cell type specifically.

[0039] For example, a non-exhaustive list of "Therapeutic protein" portions which may be comprised by an albumin fusion protein of the invention includes, but is not limited to, GLP-1, GLP-2, PACAP-27, PACAP-28, VIP, CD4M33, secretin, glicentin, oxyntomodulin, PHM, IFNα, IFNβ, ANP, BNP, NGF, BDNF, GDNF, and somatostatin.

[0040] Interferon hybrids may also be fused to the amino or carboxy terminus of albumin to form an interferon hybrid albumin fusion protein. Interferon hybrid albumin fusion protein may have enhanced, or alternatively, suppressed interferon activity, such as antiviral responses, regulation of cell growth, and modulation of immune response (Lebleu et al., *PNAS* USA, 73:3107-3111 (1976); Gresser et al., *Nature*, 251:543-545 (1974); and Johnson, *Texas Reports Biol Med*, 35:357-369 (1977)). Each interferon hybrid albumin fusion protein can be used to treat, prevent, or ameliorate viral infections (*e.g.*, hepatitis (*e.g.*, HCV); or HIV), multiple sclerosis, or cancer.

[0041] In one embodiment, the interferon hybrid portion of the interferon hybrid albumin fusion protein comprises an interferon alpha-interferon alpha hybrid (herein referred to as an alpha-alpha hybrid). For example, the alpha-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha A fused to interferon alpha D. In a further embodiment, the A/D hybrid is fused at the common BglII restriction site to interferon alpha D, wherein the N-terminal portion of the A/D hybrid corresponds to amino acids 1-62 of

interferon alpha A and the C-terminal portion corresponds to amino acids 64-166 of interferon alpha D. For example, this A/D hybrid would comprise the amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRX$_1$ISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFTTKDSSAAWDEDLLDKFCTELYQQL NDLEACVMQEERVGETPLMNX$_2$DSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE (SEQ ID NO:99), wherein the X$_1$ is R or K and the X$_2$ is A or V (see, for example, Construct ID #2875). In an additional embodiment, the A/D hybrid is fused at the common PvuII restriction site, wherein the N-terminal portion of the A/D hybrid corresponds to amino acids 1-91 of interferon alpha A and the C-terminal portion corresponds to amino acids 93-166 of interferon alpha D. For example, this A/D hybrid would comprise the amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRX$_1$ISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL NDLEACVMQEERVGETPLMNX$_2$DSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE (SEQ ID NO:100), wherein the X$_1$ is R or K and the second X$_2$ is A or V (see, for example, Construct ID #2872). These hybrids are further described in U.S. Patent No. 4,414,510, which is hereby incorporated by reference in its entirety.

[0042] In an additional embodiment, the alpha-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha A fused to interferon alpha F. In a further embodiment, the A/F hybrid is fused at the common PvuII restriction site, wherein the N-terminal portion of the A/F hybrid corresponds to amino acids 1-91 of interferon alpha A and the C-terminal portion corresponds to amino acids 93-166 of interferon alpha F. For example, this A/F hybrid would comprise the amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRXISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL NDMEACVIQEVGVEETPLMNVDSILAVKKYFQRITLYLTEKKYSPCAWEVVRAEIMRSFSLSKIFQERLRRKE (SEQ ID NO:101), wherein X is either R or K (see, for example, Construct ID #2874). These hybrids are further described in U.S. Patent No. 4,414,510, which is hereby incorporated by reference in its entirety. In a further embodiment, the alpha-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha A fused to interferon alpha B. In an additional embodiment, the A/B hybrid is fused at the common PvuII restriction site, wherein the N-terminal portion of the A/B hybrid corresponds to amino acids 1-91 of interferon alpha A and the C-terminal portion corresponds to amino acids 93-166 of interferon alpha B. For example, this A/B hybrid would comprise an amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRX$_1$ISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL NDLEX$_2$X$_3$X$_4$X$_5$QEVGVIESPLMYEDSILAVRKYFQRITLYLTEKKYSSCAWEVVRAEIMRSFSLSINLQKRLKSKE (SEQ ID NO:102), wherein the X$_1$ is R or K and X$_2$ through X$_5$ is SCVM or VLCD (see, for example, Construct ID #2873). These hybrids are further described in U.S. Patent No. 4,414,510, which is hereby incorporated by reference in its entirety.

[0043] In another embodiment, the interferon hybrid portion of the interferon hybrid albumin fusion protein comprises an interferon beta-interferon alpha hybrid (herein referred to as a beta-alpha hybrid). For example, the beta-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon beta-1 fused to interferon alpha D (also referred to as interferon alpha-1). In a further embodiment, the beta-1/alpha D hybrid is fused wherein the N-terminal portion corresponds to amino acids 1-73 of interferon beta-1 and the C-terminal portion corresponds to amino acids 74-167 of interferon alpha D. For example, this beta-1/alpha D hybrid would comprise an amino acid sequence:

MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSAAWDEDLLDKFCTELY QQLNDLEACVMQEERVGETPLMNXDSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE (SEQ ID NO:103), wherein X is A or V. These hybrids are further described in U.S. Patent No. 4,758,428, which is hereby incorporated by reference in its entirety.

[0044] In another embodiment, the interferon hybrid portion of the interferon hybrid albumin fusion protein comprises an interferon alpha-interferon beta hybrid (herein referred to as a alpha-beta hybrid). For example, the alpha-beta hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha D (also referred to as interferon alpha-1) fused to interferon beta-1. In a further embodiment, the alpha D/beta-1 hybrid is fused wherein the N-terminal portion corresponds to amino acids 1-73 of interferon alpha D and the C-terminal portion corresponds to amino acids 74-166 of interferon beta-1. For example, this alpha D/beta-1 hybrid would have an amino acid sequence:

MCDLPETHSLDNRRTLMLLAQMSRISPSSCLMDRHDFGFPQEEFDGNQFQKAPAISVLHELIQQIFNLFTTKDSSSTGWNETIVENLLANVY HQINHLKTVLEEKLEKEDFTRGKLMSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYLRN (SEQ ID NO:104). These hybrids are further described in U.S. Patent No. 4,758,428, which is hereby incorporated by reference in its entirety.

[0045] In further embodiments, the interferon hybrid portion of the interferon hybrid albumin fusion proteins may comprise additional combinations of alpha-alpha interferon hybrids, alpha-beta interferon hybrids, and beta-alpha interferon hybrids. In additional embodiments, the interferon hybrid portion of the interferon hybrid albumin fusion protein may be modified to include mutations, substitutions, deletions, or additions to the amino acid sequence of the interferon hybrid. Such modifications to the interferon hybrid albumin fusion proteins may be made, for example, to improve levels of production, increase stability, increase or decrease activity, or confer new biological properties.

[0046] The above-described interferon hybrid albumin fusion proteins are encompassed by the invention, as are host cells and vectors containing polynucleotides encoding the polypeptides. In one embodiment, a interferon hybrid albumin fusion protein encoded by a polynucleotide as

described above has extended shelf life. In an additional embodiment, a interferon hybrid albumin fusion protein encoded by a polynucleotide described above has a longer serum half-life and/or more stabilized activity in solution (or in a pharmaceutical composition) *in vitro* and/or *in vivo* than the corresponding unfused interferon hybrid molecule.

[0047] In another non-limiting example, a "Therapeutic protein" is a protein that has a biological activity, and in particular, a biological activity that is useful for treating, preventing or ameliorating a disease. A non-inclusive list of biological activities that may be possessed by a Therapeutic protein includes, inhibition of HIV-1 infection of cells, stimulation of intestinal epithelial cell proliferation, reducing intestinal epithelial cell permeability, stimulating insulin secretion, induction of bronchodilation and vasodilation, inhibition of aldosterone and renin secretion, blood pressure regulation, promoting neuronal growth, enhancing an immune response, enhancing inflammation, suppression of appetite, or any one or more of the biological activities described in the "Biological Activities" section below and/or as disclosed for a given Therapeutic protein in Table 1 (column 2).

[0048] In one embodiment, IFN-beta-HSA fusions are used to inhibit the activity of Ebola virus and the SARS virus (Toronto-2 strain). For example, the in vitro antiviral activity of IFN-beta fused upstream of mature HSA (CID 2053 protein) was evaluated against Ebola virus and SARS virus in Vero cells. These cells were used to assess the protective effects of CID 2053 protein based on inhibition of cytopathic effect (CPE) and the neutral red assay of cell viability. In vitro signal transduction was assessed by analysis of gene expression. Further, the pharmacokinetics and pharmacodynamics of CID 2053 protein were evaluated in rhesus monkeys. The results indicate that potent in vitro antiviral activity was achieved with a favorable safety index. The IC50 for CID 2053 protein was 0.4 ng/ml against Ebola and 2 ng/ml against the SARS virus. Array analysis showed that CID 2053 protein and IFN-beta induce the expression of a similar set of genes and trigger the IFN-stimulated response element (ISRE) signal transduction pathway. In rhesus monkeys administered a dose of 50 ug/kg IV or SC or 300 ug/kg SC CID 2053 protein, the terminal half-life was 36-40 hours. Administration of CID 2053 protein induced sustained increases in serum neopterin levels and OAS1 mRNA expression.

[0049] In a further embodiment, IFN-alpha-HSA fusions are used to inhibit viral agents classified under Category A- Filo (Ebola), Arena (Pichende), Category B- Toga (VEE) or Category C- Bunya (Punto toro), Flavi (Yellow fever, West Nile). For example, CPE inhibition, neutral red staining and virus yield assays were employed to evaluate the antiviral activities of INF-alpha fused downstream of HSA (CID 3165 protein). The pharmacokinetics and pharmacodynamic activity of CID 3165 protein in cynomolgus monkeys and human subjects were evaluated. The results indicate that antiviral activity was achieved against all the RNA viruses evaluated with a favorable safety index. The IC50 values ranged from <0.1 ng/ml (Punta Toro A) to 19 ng/ml (VEE) in the CPE assay. In cynomolgus monkeys, the half-life of CID 3165 protein was 90 hours and was detectable up to 14 days post-dose. In human subjects, CID 3165 protein was safe and well tolerated. C_{max} following single injection doses was dose-proportional. The mean C_{max} in the 500 ug cohort was 22 ng/ml, and the mean $t_{1/2}$ was 150 hours. Dosing once every 2-4 weeks or more is supported by the pharmacokinetics. Antiviral response against Hepatitis C was observed in the majority of subjects in the single injection cohorts (120-500 ug).

[0050] In a further embodiment, IFN-alpha-HSA fusions are used to treat patients with chronic Hepatitis C infection (HCV). Interferon alpha, also known as interferon alfa or leukocyte inferon, is the standard of care for treatment of patients infected with HCV. The term "interferon alpha" refers to a family of highly homologous related polypeptides with anti-viral activity. The interferon alpha portion of the IFN-alpha-HSA fusion consists or alternatively comprises any interferon alpha or fragment thereof known in the art. Non-limiting examples of interferon alpha encompassed by the invention include, but are not limited to, the interferon alpha proteins disclosed in the Therapeutic protein column of Table 1. In particular embodiments, the interferon alpha portion consists or alternatively comprises interferon alpha-2a, interferon alpha-2b, interferon alpha-2c, consensus interferon, interferon alfacon-1, interferon alpha-n1, interferon alpha-n3, any commercially available form of interferon alpha, such as, for example, INTRON® A (Schering Corp., Kenilworth, N.J.), ROFERON® A (Hoffman-La Roche, Nutley, N.J.), Berofor alpha inteferon (Boehringer Ingelheim Pharmaceutical, Inc., Ridgefied, Conn.), OMNIFERON™ (Viragen, Inc., Plantation, FL), MULTIFERON™ (Viragen, Inc., Plantation, FL) WELLFERON® (GlaxoSmithKline, London, Great Britian), INFERGEN® (Amgen, Inc., Thousands Oaks, CA), SUMIFERON® (Sumitomo, Japan), BELEROFON® (Nautilus Biotech, France) or any purified interferon alpha product or a fragment thereof. In additional embodiments, the interferon alpha portion of the IFN-alpha-HSA fusion protein may be modified by the attachment of chemical moieties. For example, the inteferon alpha portion may be modified by pegylation. Accordingly, in additional embodiments, the interferon alpha portion of the IFN-alpha-HSA fusion protein consists or alternatively comprises pegylated forms of interferon alpha-2a, 2b, or consensus interferon and include, but are not limited to, a commercially available pegylated interferon alpha, such as, for example, PEG-INTRON® (Schering Corp., Kenilworth, N.J.), PEGASYS® (Hoffman-La Roche, Nutley, N.J.), PEG-OMNIFERON™ (Viragen, Inc., Plantation, FL) or a fragment thereof. However, as used herein, "IFN-alpha-HSA" fusions refers to the HSA fused to any of the interferon alpha proteins known in the art or a fragment thereof.

[0051] Patients infected with HCV may fall within two categories based on previous exposure to an interferon regimen for treatment of the HCV infection. "Naive patients" are those patients who have never been treated with an interferon regimen. "Experienced patients" are those patients who have been treated or are currently being treated with an interferon regimen. "Non-responders" are experienced patients who have been previously treated with an interferon regimen but have failed to meet the primary endpoint of treatment such as an early viral load reduction (EVR) or an end-of-treatment response (ETR). However, as used herein, an "HCV patient" refers to a patient who is infected with HCV and who is either

naive, experienced, or a non-responder.

[0052] In addition, the Hepatitis C virus can be classified into four genotypes, genotype 1, 2, 3, or 4. Generally, the Hepatitis C virus that infects an HCV patient comprises a single genotype. However, the Hepatitis virus can comprise a combination of two or more genotypes. In addition, the genotype of Hepatitis C virus may also be a variant of one of the known HCV genotypes. In a further embodiment, the Hepatitis C virus of the HCV patient is genotype 1 or a variant thereof. However, as used herein, "HCV" refers to the Hepatitis C virus of any genotype, or combination or variants thereof.

[0053] The standard treatment regimen for patients with HCV involves treatment with interferon alpha in combination with an antiviral agent, such as, ribavirin. In general, the interferon alpha is administered daily, twice-a-week, or weekly and the ribavirin is administered daily. However, recent studies have also used inteferon alpha in combination with other antiviral agents known in the art for the treatment of HCV. Thus, in a further embodiment the IFN-alpha-HSA fusion may be administered to the HCV patient either alone or in combination with an antiviral agent, such as, for example, ribavirin.

[0054] As noted above, pharmokinetics of the CID 3165 protein support a dosing schedule of once every 2-4 weeks or greater. Thus, in a further embodiment, the HCV patients are treated with an IFN-alpha-HSA fusion by administration once every 2-4 weeks alone or in combination with an effective amount of an antiviral agent. In a preferred embodiment, the HCV patients are treated with an IFN-alpha-HSA fusion by administration once every 2-4 weeks in combination with an effective amount of an antiviral agent. In an additional preferred embodiment, the IFN-alpha-HSA fusion is administered to the HCV patient once every 4 weeks. In an additional preferred embodiment, the IFN-alpha-HSA fusion is administered to the HCV patient more than once every 4 weeks. In additional embodiments, the IFN-alpha-HSA fusion is adminstered once every 4 weeks or more to an HCV patient, wherein the treatment also includes administration of an effective amount of an antiviral agent.

[0055] In a another embodiment, IFN-alpha-HSA fusions may be used as a low-dose monotherapy for maintenance therapy of HCV. In a further additional embodiment, IFN-alpha-HSA fusions may used in combination with ribavirin and one or more other antiviral agents for the treatement of HCV. Alternatively, in another embodiment, IFN-alpha-HSA fusions may be used in combination with one or more antiviral agents, other than ribavirin, for the treatment of HCV.

[0056] In an additional embodiment, IFN-alpha-HSA fusions may be used for the treatment of other viral infections. For example, in one embodiment, IFN-alpha-HSA fusions may be used for the treatment of Hepatitis B (HBV). In an additional embodiment, IFN-alpha-HSA fusions may be used for the treatment of Human Papilloma Virus (HPV). In a further embodiment, IFN-alpha-HSA fusions may be used in the treatment of cancer, including, but not limited to hairy cell leukemia, malignant melanoma, follicular lymphoma, chronic myelogenous leukemia, AIDS related Kaposi's Sarcoma, multiple myeloma, or renal cell cancer.

[0057] In another embodiment, GLP-1-HSA fusions are used to regulate blood glucose levels in diabetic patients. In a further embodiment, tandem fusions of wild-type or mutant GLP-1 are used to regulate blood glucose levels in diabetic patients. For example, the ability of monomer GLP-1(7-36A8G)-HSA and tandem GLP-1(7-36A8G)-HSA (CID 3610) fusions to regulate the blood glucose levels were evaluated utilizing an oral glucose tolerance test (1 gram glucose/kg by oral gavage), following subcutaneous injection of GLP-1-HSA protein in ~8 week old diabetic db/db mice. This glucose tolerance test consisted of the subcutaneous injection of a GLP-1-HSA fusion followed by administration of 1 gram glucose/kg by oral gavage. Fasted diabetic db/db mice were administered equimolar doses (100 and 171 nmol/kg) of either the monomer or tandem GLP-1-HSA fusion protein and oral glucose tolerance tests were performed 6 or 24 hours after a single administration. Quite surprisingly and unexpected, the tandem GLP-1(7-36A8G)-HSA fusion (CID 3610) significantly reduced blood glucose at 6 hours after injection when compared to the monomer GLP-1(7-36A8G)-HSA fusion. In addition, the difference between monomer GLP-1(7-36A8G)-HSA and tandem GLP-1(7-36A8G)-HSA (CID 3610) fusions were even more dramatic when diabetic db/db mice were evaluated 24 hours after injection. As shown in Figure 11, the tandem GLP-1(7-36A8G)-HSA fusion (CID 3610) (◇) possessed a unexpectedly potent glucose-normalizing activity while fasting blood glucose levels for the single GLP-1(7-36A8G)-HSA (△) fusion was similar to animals administered HSA alone (●) and clearly were diabetic in nature.

[0058] As used herein, "therapeutic activity" or "activity" may refer to an activity whose effect is consistent with a desirable therapeutic outcome in humans, or to desired effects in non-human mammals or in other species or organisms. Therapeutic activity may be measured *in vivo* or *in vitro*. For example, a desirable effect may be assayed in cell culture. Such *in vitro* or cell culture assays are commonly available for many Therapeutic proteins as described in the art. Examples of assays include, but are not limited to those described herein in the Examples section or in the "Exemplary Activity Assay" column (column 3) of Table 1.

[0059] Therapeutic proteins corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention, such as cell surface and secretory proteins, are often modified by the attachment of one or more oligosaccharide groups. The modification, referred to as glycosylation, can dramatically affect the physical properties of proteins and can be important in protein stability, secretion, and localization. Glycosylation occurs at specific locations along the polypeptide backbone. There are usually two major types of glycosylation: glycosylation characterized by O-linked oligosaccharides, which are attached to serine or threonine residues; and glycosylation characterized by N-linked oligosaccharides, which are attached to asparagine residues in an Asn-X-Ser or Asn-X-Thr sequence, where X can be any amino acid except proline. N-acetylneuramic acid (also known as sialic acid) is usually the terminal residue of both N-linked and 0-linked oligosaccharides. Variables such as protein structure and

cell type influence the number and nature of the carbohydrate units within the chains at different glycosylation sites. Glycosylation isomers are also common at the same site within a given cell type.

[0060] Therapeutic proteins corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention, as well as analogs and variants thereof, may be modified so that glycosylation at one or more sites is altered as a result of manipulation(s) of their nucleic acid sequence, by the host cell in which they are expressed, or due to other conditions of their expression. For example, glycosylation isomers may be produced by abolishing or introducing glycosylation sites, *e.g.*, by substitution or deletion of amino acid residues, such as substitution of glutamine for asparagine, or unglycosylated recombinant proteins may be produced by expressing the proteins in host cells that will not glycosylate them, *e.g.* in *E. coli* or glycosylation-deficient yeast. These approaches are described in more detail below and are known in the art.

[0061] Therapeutic proteins, particularly those disclosed in Table 1, and their nucleic acid and amino acid sequences are well known in the art and available in public databases such as Chemical Abstracts Services Databases (e.g., the CAS Registry), GenBank, and subscription provided databases such as GenSeq (e.g., Derwent). Exemplary nucleotide sequences of Therapeutic proteins which may be used to derive a polynucleotide of the invention are shown in column 7, "SEQ ID NO:X," of Table 2. Sequences shown as SEQ ID NO:X may be a wild type polynucleotide sequence encoding a given Therapeutic protein (e.g., either full length or mature), or in some instances the sequence may be a variant of said wild type polynucleotide sequence (*e.g.*, a polynucleotide which encodes the wild type Therapeutic protein, wherein the DNA sequence of said polynucleotide has been optimized, for example, for expression in a particular species; or a polynucleotide encoding a variant of the wild type Therapeutic protein (i.e., a site directed mutant; an allelic variant)). It is well within the ability of the skilled artisan to use the sequence shown as SEQ ID NO:X to derive the construct described in the same row. For example, if SEQ ID NO:X corresponds to a full length protein, but only a portion of that protein is used to generate the specific CID, it is within the skill of the art to rely on molecular biology techniques, such as PCR, to amplify the specific fragment and clone it into the appropriate vector.

[0062] Additional Therapeutic proteins corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention include, but are not limited to, one or more of the Therapeutic proteins or peptides disclosed in the "Therapeutic Protein X" column of Table 1 (column 1), or fragment or variable thereof.

[0063] Table 1 provides a non-exhaustive list of Therapeutic proteins that correspond to a Therapeutic protein portion of an albumin fusion protein of the invention, or an albumin fusion protein encoded by a polynucleotide of the invention. The first column, "Therapeutic Protein X," discloses Therapeutic protein molecules that may be followed by parentheses containing scientific and brand names of proteins that comprise, or alternatively consist of, that Therapeutic protein molecule or a fragment or variant thereof. "Therapeutic protein X" as used herein may refer either to an individual Therapeutic protein molecule, or to the entire group of Therapeutic proteins associated with a given Therapeutic protein molecule disclosed in this column. The "Biological activity" column (column 2) describes Biological activities associated with the Therapeutic protein molecule. Column 3, "Exemplary Activity Assay," provides references that describe assays which may be used to test the therapeutic and/or biological activity of a Therapeutic protein:X or an albumin fusion protein comprising a Therapeutic protein X (or fragment thereof) portion. Each of the references cited in the "Exemplary Activity Assay" column are herein incorporated by reference in their entireties, particularly with respect to the description of the respective activity assay described in the reference (see Methods section therein, for example) for assaying the corresponding biological activity set forth in the "Biological Activity" column of Table 1. The fourth column, "Preferred Indication: Y," describes disease, disorders, and/or conditions that may be treated, prevented, diagnosed, and/or ameliorated by Therapeutic protein X or an albumin fusion protein comprising a Therapeutic protein X (or fragment thereof) portion. The "Construct ID" column (column 5) provides a link to an exemplary albumin fusion construct disclosed in Table 2 which encodes an albumin fusion protein comprising, or alternatively consisting of the referenced Therapeutic Protein X (or fragment thereof) portion.

Table 1

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Construct ID	Therapeutic Protein:Z
Human growth hormone (Pegvisamont; Somatrem; Somatropin; TROVERT; PROTROPIN; BIO-TROPIN; HUMATROPE; NUTROPIN; NUTROPIN AQ; NUTROPHIN; NORDITROPIN; GENOTROPIN; SAIZEN; SEROSTIM)	Binds to two GHR molecules and Induces signal transduction through receptor dimerization	Ba/F3-hGHR proliferation assay, a novel specific bioassay for serum human growth hormone. J Clin Endocrinol Metab 2000 Nov;85(11):4274-9 Plasma growth hormone (GH) immunoassay and tibial bioassay, Appl Physiol 2000 Dec;89(6):2174-8 Growth hormone (hGH) receptor mediated cell mediated proliferation, Growth Horm IGF Res 2000 Oct;10(5):248-55 International standard for growth hormone, Horm Res 1999;51 Suppl 1:7-12	Acromegaly; Growth failure; Growth hormone replacement; Growth hormone deficiency; Pediatric Growth Hormone Deficiency; Adult Growth Hormone Deficiency; Idiopathic Growth Hormone Deficiency; Growth retardation; Prader-Willi Syndrome; Prader-Willi Syndrome in children 2 years or older; Growth deficiencies; Growth failure associated with chronic renal insufficiency; Osteoporosis; Postmenopausal osteoporosis; Osteopenia, Osteoclastogenesis; burns; Cachexia; Cancer Cachexia; Dwarfism; Metabolic Disorders; Obesity; Renal failure; Turner's Syndrome; Fibromyalgia; Fracture treatment; Frailty, AIDS wasting; Muscle Wasting; Short Stature; Diagnostic Agents; Female Infertility; lipodystrophy.	3468, 3469, 3470, 3475.	See Table 2, SEQ ID NO:Z for particular construct.
Interferon alpha (Interferon alfa-2b; recombinant; Interferon alfa-n1; Interferon alfa-n3; Peginterferon alpha-2b; Ribavirin and interferon alfa-2b; Interferon alfacon-1; interferon consensus; YM 643; CIFN; interferon -alpha consensus; recombinant methionyl consensus interferon; recombinant consensus interferon; CGP 35269; RO 253036; RO 258310; INTRON A; PEG-INTRON; OIF; OMNIFERON; PEG-OMNIFERON; VELDONA; PEG-REBETRON; ROFERON A; WELLFERON; ALFERON N/LDO; REBETRON; ALTEMOL; VIRAFERONPEG; PEGASYS; VIRAFERON; VIRAFON; AMPLIGEN; INFERGEN; INFAREX; ORAGEN)	Confers a range of cellular responses including antiviral, antiproliferative, antitumor and immunomodulatory activities; stimulate production of two enzymes: a protein kinase and an oligoadenylate synthetase.	Anti-viral assay: Rubinstein S, Familletti PC, Pestka S. (1981) Convenient assay for interferons. J. Virol. 37(2):755-8; Anti-proliferation assay: Gao Y, et al (1999) Sensitivity of an epstein-barr virus-positive tumor line, Daudi, to alpha interferon correlates with expression of a GC-rich viral transcript. Mol Cell Biol. 19(11):7305-13.	Viral infections include Severe Acute Respiratory Syndrome (SARS) and other coronavirus infections; filoviruses, including but not limited to Ebola viruses and Marburg virus; Arenaviruses, including but not limited to Pichende virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus; and lymphocytic choriomeningitis virus (LCMV); Bunyaviruses, including but not limited to Punta toro virus, Crimean-Congo hemorrhagic fever virus, sandfly fever viruses, Rift Valley fever virus, La Crosse virus, and hantaviruses; Flaviviruses, including but not limited to Yellow Fever, Banzi virus, West Nile virus, Dengue viruses, Japanese Encephalitis virus, Tick-borne encephalitis, Omsk Hemorrhagic Fever, and Kyasanur Forest Disease virus; Togaviruses, including but not limited to Venezuelan, eastern, and western equine encephalitis viruses, Ross River virus, and Rubella virus; Orthopox viruses, including but not limited to Vaccinia, Cowpox, Smallpox, and Monkeypox; Herpesviruses; FluA/B; Respiratory Sincytial virus (RSV); paraflu; measles; rhinoviruses; adenoviruses; Semliki Forest virus; Viral Hemorrhagic fevers; Rhabdoviruses; Paramyxoviruses, including but not limited to Nipah virus and Hendra virus; and other viral agents identified by the U.S. Centers for Disease Control and Prevention as high-priority disease agents (*i.e.*, Category A, B, and C agents; see, *e.g.*, Moran, Emerg. Med. Clin. North. Am. 2002; 20(2):311-30	2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476.	See Table 2, SEQ ID NO:Z for particular construct.

Table 1

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Construct ID	Therapeutic Protein:Z
			and Darling et al., Emerg. Med. Clin. North Am. 2002;20(2):273-309).		
Interferon beta (Interferon beta-1a; Interferon beta 1b; Interferon-beta-serine; SH 579; ZK 157046; BCDF; beta-2 IF; Interferon-beta-2; rhIL-6; SJ0031; DL 8234; FERON; IFNbeta; BETASERON; AVONEX; REBIF; BETAFERON; SIGOSIX)	Modulates MHC antigen expression, NK cell activity and IFNg production and IL12 production in monocytes.	Anti-viral assay: Rubinstein S, Familletti PC, Pestka S. (1981) Convenient assay for interferons. J. Virol. 37(2):755-8; Anti-proliferation assay: Gao Y, et al (1999) Sensitivity of an epstein-barr virus-positive tumor line, Daudi, to alpha interferon correlates with expression of a GC-rich viral transcript. Mol Cell Biol. 19(11):7305-13.	Viral infections include Severe Acute Respiratory Syndrome (SARS) and other coronavirus infections; filoviruses, including but not limited to Ebola viruses and Marburg virus; Arenaviruses, including but not limited to Pichende virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus; and lymphocytic choriomeningitis virus (LCMV); Bunyaviruses, including but not limited to Punta toro virus, Crimean-Congo hemorrhagic fever virus, sandfly fever viruses, Rift Valley fever virus, La Crosse virus, and hantaviruses; Flaviviruses, including but not limited to Yellow Fever, Banzi virus, West Nile virus, Dengue viruses, Japanese Encephalitis virus, Tick-borne encephalitis, Omsk Hemorrhagic Fever, and Kyasanur Forest Disease virus; Togaviruses, including but not limited to Venezuelan, eastern, and western equine encephalitis viruses, Ross River virus, and Rubella virus; Orthopox viruses, including but not limited to Vaccinia, Cowpox, Smallpox, and Monkeypox; Herpesviruses; FluA/B; Respiratory Sincytial virus (RSV); paraflu; measles; rhinoviruses; adenoviruses; Semliki Forest virus; Viral Hemorrhagic fevers; Rhabdoviruses; Paramyxoviruses, including but not limited to Nipah virus and Hendra virus; and other viral agents identified by the U.S. Centers for Disease Control and Prevention as high-priority disease agents (*i.e.*, Category A, B, and C agents; see, *e.g.*, Moran, Emerg. Med. Clin. North. Am. 2002; 20(2):311-30 and Darling et al., Emerg. Med. Clin. North Am. 2002;20(2):273-309).	1778, 1779, 2011, 2013, 2053, 2054, 2492, 2580, 2795, 2796, 2797.	See Table 2, SEQ ID NO:Z for particular construct.
B-type natriuretic peptide (BNP, brain natriuretic peptide)	stimulates smooth muscle relaxation and vasodilation, natriuresis,and suppression of renin-angiotensin and endothelin.	Inhibition of angiotensin can be determined using assays known in the art, for example using an in vitro proliferation assay with rat cardiac fibroblasts as described in Naunyn Schmiedebergs Arch Pharmacol 1999 May;359(5):394-9. Vasodilation can be measured in animals by measuring the	Congestive heart failure; cardiac volume overload; cardiac decompensation; Cardiac Failure; Left Ventricular Dysfunction; Dyspnea. Glomerular hypertrophy; Glomerular injury; Renal glomerular disease; Acute Renal Failure.	3618, 3690, 3691, 3715, 3723, 3724, 3725, 3736, 3769, 3778, 3783, 3795, 3796, 3809,	See Table 2, SEQ ID NO:Z for particular construct.

Table 1

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Construct ID	Therapeutic Protein:Z
		myogenic responses of small renal arteries in an isobaric arteriograph system (*see* Am J Physiol Regul Integr Comp Physiol 2002 Aug;283(2):R349-R355). Natriuesis is determined by measuring the amount of sodium in the urine.		3896, 3897, 3898, 3899, 3900.	
BDNF isoform c (brain-derived neurotrophic factor)	Neurotrophic factor that promotes neuronal growth, differentiation, and survival; maintains the survival of subsets of peripheral and central neurons during development; plays a role in a adult nervous system function; may contribute to the nociceptive responses.	BDNF activity on neuronal growth can be measured using neuronal growth and synaptic activity assays, such as those described in Bartrup et al (1997) Neuroreport 1:8(17):3791-4; BDNF activity on pain reception can be assayed by measuring nociceptive behaviors, hyperalgesia, and/or allodynia as described in Shu et al Pain (1999) 80:463-470 and in Zhou et al Eur. J. Neurosci. (2000) 12:100-105.	Pain; Neuropathic pain; Complex regional pain syndrome I; Reflex sympathetic dystrophy; Trigeminal neuralgia; Allodynia; Primary and/or Secondary hyperalgesia; Causalgia; Phantom limb pain; Post-surgical pain; Burning feet syndrome; Guillain-Barre syndrome; Thalamic syndrome; Post-stroke pain; Vasculitic/ angiopathic pain; Idiopathic pain; Pain associated with any of the following: Entrapment neuropathy, Nerve transection, Spinal cord injury, Scar formation, Alcoholic neuropathy, Pellagra, Beriberi, Post-herpetic neuralgia, HIV/AIDS pain, Vincristine neurotoxicity, Cisplatin neurotoxicity, Taxol neurotoxicity, Thallium neurotoxicity, Arsenic neurotoxicity, Radiation therapy, Diabetes, Malignancies, Multiple sclerosis, Fabry's disease, Tangier disease, or Amyloid.	3549.	See Table 2, SEQ ID NO:Z for particular construct.
Glucagon-Like-Peptide 1 (GLP1; GLP-1; Insulinotropin)	Stimulates the synthesis and release of insulin; enhances the sensitivity of adipose, muscle, and liver tissues towards insulin; stimulates glucose uptake; slows the digestive process; suppresses appetite; blocks the secretion of glucagon.	GLP1 activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873). GLP-1 effects on learning can be investigated using the possive avoidance and Morris water maze (MWM) paradigms in rats (Brain Res. 1996, 716:29-38 and Nature 1982, 297:681-683).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X; Cognitive Impairment; Memory Loss. Use to enhance learning, memory, associative learning, spatial learning, hippocampal plasticity, cognition, and/or neuroprotection.	3610, 3696.	See Table 2, SEQ ID NO:Z for particular construct.
Lysosomal glucocerebrosidase; (Alglucerase; β-glucocerebrosidase; β-D-glucosyl-*N*-acylsphingosine glucohyrdolase; Glucosylceramidase; acid β-	Catalyzes the hydrolysis of D-glucosyl-*N*-acylsphingosine to D-glucose and N-acylsphingosine, catalyzes the hydrolysis of glucocerebroside to glucose ceramide	Enzymatic activity can be assessed using methods known in the art, for example, the thin-layer chromatography assay described by Poulos et al., Clin. Chim. Acta. 1976 Nov; 72(3):327-335; or the FACS method described by Rudensky et al., Blood Cells Mol. Dis. 2003	Gaucher disease, lysosomal storage diseases	3920; 3921; 3922; 3923.	See Table 2, SEQ ID NO:Z for particular construct. Also, for particular lysosomal glucocerebrosidase sequences or variant

Table 1

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Construct ID	Therapeutic Protein:Z
glucosidase; Imiglucerase; CEREDASE; CEREZYME) (GCB)		Jan-Feb; 30(1):97-99.			thereof, see GLCM_HUMAN, Genbank Accession No. P04062; CAS-143003-46-7, each of which is incorporated by reference. Other lysosomal glucocerebrosidase sequence are disclosed in U.S. Patent Pub Nos. 20040009165; 20030133924; 20020127219, each of which is incorporated by reference. Additional lysosomal glucocerebrosidases are disclosed in U.S. Patent Nos. 6,696,272; 5,879,680; 5,549,892, each of which is incorporated by reference.
Arginine deiminase (ADI-SS)	Catalyzes the irreversible hydrolysis of arginine to citrulline and ammonia; inhibits nitric oxide synthesis; inhibits angiogenesis; inhibits proliferation of numerous tumor cells.	Enzymatic activity can be measured using methods well known in the art, such as the enzyme assay described in Weickmann et al., J. Biol. Chem. 1977 Apr; 252(8):2615-2620. Inhibition of angiogenesis can be assessed using known methods in the art, for example, the Matrigel assay as described in Park et al., Br. J. Cancer 2003 Sept; 89(5):907-914. Inhibition of nitric oxide production can be assessed using known methods in the art, for example, as described in Noh et al., Mol. Cells 2002 Feb:13(1):137-143. Tumor cell proliferation can be assessed using known methods in the art, for example, the proliferation assay as described in Miyazaki et al., Cancer Res. 1990 Aug; 50(15):4522-4527.	Cancer, including but not limited to melanoma and hepatocellular carcinoma. Additional cancers include, but are limited to, squamous cell carcinom; osteosarcoma, glioma/astrocytoma; glioblatoma, premyelocytic leukemia; lymphoblastic leukemia; and carcinomas of the cervix, breast, ovaries, prostate, colon, or lung.	3910, 3915, 3917, 3918.	See Table 2, SEQ ID NO:Z for particular construct. Also, for particular arginine deiminase sequence or variant thereof, see Baur et al., Eur. J. Biochem 1989 Jan; 179(1):53-60; Misawa et al., J. Biotechnol. 1994; 361:145-155; each of which is incorporated by reference. Other arginine deiminase sequences are disclosed in U.S. Patent Pub No. 20040096437, incorporated by reference. Other arginine deiminases are disclosed in, U.S. Patent Nos. 6,180,387; 5,804,183; 5,474,928; 5,196,195, each of which

Table 1

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Construct ID	Therapeutic Protein:Z
					is incorporated by reference.
Uricase (Urate oxidase; *Aspergillis flavus* uricase; *Candida utilis* uricase; rasburicase; FASTURTEC; ELITEK)	Catalyzes the oxidation of uric acid into allantoin	Levels of uric acid can be measured spectrophotometrically, colormetrically or using other methods that are well known in the art, such as in Kageyama, Clin. Chim. Acta. 1971; 31(2):421-426.	Gout; hyperuricemia; tumor lysis hyperurecia; chemotherapy-induced hyperurecia; ischemic stroke; lipid abnormalities; cardiovascular disorders, including but not limited to hypertension, coronary artery disease, atherosclerosis.	3903, 3904, 3936, 3937, 3938, 3939, 3940, 3941, 3942, 3943, 3944.	See Table 2, SEQ ID NO:Z for particular construct. Also, for particular uricase sequence or variant thereof, see CAS-134774-45.1; Wu et al., P.N.A.S. USA 1989 Dec; 86(23):9412-9416; each of which is incorporated by reference. Other uricase sequences are disclosed in U.S. Patent Nos. 4,062,731; 4,273,874; 4,987,076; 5,376,545; 5,700,674; 5,728,562; 5,801,036; 5,834,273; 5,955,336; each of which is incorporated by reference
Interferon Hybrids, specifically preferred: IFNalpha A/D hybrid (BglII version) IFNalpha A/D hybrid (PvuII version) IFNalpha A/F hybrid IFNalpha A/B hybrid IFNbeta 1/alpha D hybrid (IFNbeta-1/alpha-1 hybrid) IFNalpha/beta hybrid	Confers a range of cellular responses including antiviral, antiproliferative, antitumor and immunomodulatory activities; stimulate production of two enzymes: a protein kinase and an oligoadenylate synthetase. Also, modulates MHC antigen expression, NK cell activity and IFNg production and IL12 production in monocytes.	Anti-viral assay: Rubinstein S, Familletti PC, Pestka S. (1981) Convenient assay for interferons. J. Virol. 37(2):755-8; Anti-proliferation assay: Gao Y, et al (1999) Sensitivity of an epstein-barr virus-positive tumor line, Daudi, to alpha interferon correlates with expression of a GC-rich viral transcript. Mol Cell Biol. 19(11):7305-13.	Viral infections include Severe Acute Respiratory Syndrome (SARS) and other coronavirus infections; filoviruses, including but not limited to Ebola viruses and Marburg virus; Viral infections; HIV Infections; Hepatitis; Arenaviruses, including but not limited to Pichende virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus; and lymphocytic choriomeningitis virus (LCMV); Bunyaviruses, including but not limited to Punta toro virus, Crimean-Congo hemorrhagic fever virus, sandfly fever viruses, Rift Valley fever virus, La Crosse virus, and hantaviruses; Flaviviruses, including but not limited to Yellow Fever, Banzi virus, West Nile virus, Dengue viruses, Japanese Encephalitis virus, Tick-borne encephalitis, Omsk Hemorrhagic Fever, and Kyasanur Forest Disease virus; Togaviruses, including but not limited to Venezuelan, eastern, and western equine encephalitis viruses, Ross River virus, and Rubella virus; Orthopox viruses, including but not limited to Vaccinia, Cowpox, Smallpox, and Monkeypox; Herpesviruses; FluA/B; Respiratory Sincytial virus (RSV); paraflu; measles; rhinoviruses; adenoviruses; Semliki Forest virus;	2872, 2873, 2874, 2875, 2876.	See Table 2, SEQ ID NO:Z for particular construct.

Table 1

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Construct ID	Therapeutic Protein:Z
			Viral Hemorrhagic fevers; Rhabdoviruses; Paramyxoviruses, including but not limited to Nipah virus and Hendra virus; and other viral agents identified by the U.S. Centers for Disease Control and Prevention as high-priority disease agents (*i.e.*, Category A, B, and C agents; see, *e.g.*, Moran, Emerg. Med. Clin. North. Am. 2002; 20(2):311-30 and Darling et al., Emerg. Med. Clin. North Am. 2002;20(2):273-309).		
IL-2 (Aldesleukin; interleukin-2 fusion toxin; T cell growth factor; PROLEUKIN; IMMUNACE; CELEUK; ONCOLIPIN 2; MACROLIN)	Promotes the growth of B and T cells and augments NK cell and CTL cell killing activity.	T cell proliferation assay "Biological activity of recombinant human interleukin-2 produced in Escherichia coli." Science 223: 1412-1415, 1984. natural killer (NK) cell and CTL cytotoxicity assay "Control of homeostasis of CD8+ memory T cells by opposing cytokines. Science 288: 675-678, 2000; CTLL-2 Proliferation : Gillis et al (1978) J. Immunol. 120, 2027	Cancer; Solid Tumors; Pancreatic Cancer; Colon Cancer; Liver Cancer; T-lymphomas; Graft-versus-host disease (GVH); Autoimmune diseases; Autoimmune disorders; IL-2 receptor positive malignancies.	1757, 1758, 1812, 1813, 1952, 1954.	See Table 2, SEQ ID NO:Z for particular construct.
Adrenomedullin (ADM)	Inhibits renal Na+-K+-ATPase; enhances synthesis of prostaglandin E2 that regulates contraction and relaxation of smooth muscle, as well as the dilation and constriction of blood vessels; inhibits aldosterone secretion; causes diuresis and natriuresis. Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids; renoprotection.	Renal Na+-K+-ATPase activity can be measured using assays known in the art, such as in Ku et al., 1987; Endocrinology 120:2166-2173. Vasodilation can be measured using assays known in the art (Ashton et al. Pharmacology 2000; 61(2):101-105. Prostaglandin E2 synthesis can be determined using assays known in the art, (Cheng et al., J Endocrinol. 2004 Aug;182(2):249-56). Aldosterone levels can be measured using methods known in the art, for example, in Yamato et al., Circ J 2003 May; 67(5):384-90. Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., Ultrasound Med Biol 2003 Mar; 29(3):379-85. Natriuesis is determined by measuring the amount of sodium in the urine. Diuresis is determined by measuring the amount of urine secreted.	Treatment of Congestive Heart Failure; Hypertension; Cardiovascular disease; Acute renal failure; Acute tubular necrosis; Renal disease; Renal Glomerular disease; Cardiac volume overload; cardiac decompensation; Left Ventricular Dysfunction; Dyspnea. Treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiac failure; myocardial reperfusion injury; left ventricle remodeling.	3924, 3925, 3926, 3927.	See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol 2003; 285:F167-177 which is incorporated by reference
Long-acting natriuretic peptide (LANP; proANP-(31-67);	Inhibits renal Na^+-K^+-ATPase; enhances synthesis of prostaglandin E2 that regulates contraction and relaxation of smooth muscle, as well as the	Renal Na^+-K^+-ATPase activity can be measured using assays known in the art, such as in Ku et al., 1987; Endocrinology 120:2166-2173. Vasodilation can be measured using assays known in the art (Ashton et al.	Treatment of Congestive Heart Failure; Hypertension; Cardiovascular disease; Cardiac volume overload; cardiac decompensation; Left Ventricular Dysfunction; Dyspnea; Acute tubular necrosis; Acute renal failure; kidney tubule	3886, 3887.	See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol 2003; 285:F167-177 which

Table 1

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Construct ID	Therapeutic Protein:Z
	dilation and constriction of blood vessels; inhibits plasma renin activity; causes diuresis and natriuresis. Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids; renoprotection.	Pharmacology 2000; 61(2):101-105. Prostaglandin E2 synthesis can be determined using assays known in the art, (Cheng et al., J Endocrinol. 2004 Aug;182(2):249-56). Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., Ultrasound Med Biol 2003 Mar; 29(3):379-85. Natriuesis is determined by measuring the amount of sodium in the urine. Diuresis is determined by measuring the amount of urine secreted.	regeneration; Chronic Renal failure; Renal disease; Renal Glomerular disease.		is incorporated by reference
Vessel Dialator (VDP; proANP-(79-98)).	Inhibits renal Na^+-K^+-ATPase; enhances synthesis of prostaglandin E2 that regulates contraction and relaxation of smooth muscle, as well as the dilation and constriction of blood vessels; inhibits aldosterone secretion; causes natriuresis in patients with congestive heart failure; causes kaliuresis. Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids; renoprotection.	Renal Na^+-K^+-ATPase activity can be measured using assays known in the art, such as in Ku et al., 1987; Endocrinology 120:2166-2173. Vasodilation can be measured using assays known in the art (Ashton et al. Pharmacology 2000; 61(2):101-105. Prostaglandin E2 synthesis can be determined using assays known in the art, (Cheng et al., J Endocrinol. 2004 Aug;182(2):249-56). Aldosterone levels can be measured using methods known in the art, for example, in Yamato et al., Circ J 2003; May; 67(5):384-90. Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., Ultrasound Med Biol 2003 Mar; 29(3):379-85. Natriuesis is determined by measuring the amount of sodium in the urine. Kaliuresis is determined by measuring the amount of potassium in the urine.	Treatment of Congestive Heart Failure; Hypertension; Cardiovascular disease; Cardiac volume overload; cardiac decompensation; Left Ventricular Dysfunction; Dyspnea Acute tubular necrosis; Acute renal failure; Renal disease; Renal Glomerular disease. Treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiac failure; myocardial reperfusion injury; left ventricle remodeling.	3888, 3889.	See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol 2003; 285:F167-177 which is hereby incorporated by reference
Kaliuretic Peptide (KUP; proANP-(99-126)).	Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids.	Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., Ultrasound Med Biol 2003 Mar; 29(3):379-85. Natriuesis is determined by measuring the amount of sodium in the urine. Diuresis is determined by measuring the amount of urine secreted..	Treatment of Congestive Heart Failure; Hypertension; Cardiovascular disease; Acute tubular necrosis; Acute renal failure; Renal disease; Renal Glomerular disease.	3890, 3891.	See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol 2003; 285:F167-177 which is hereby incorporated by reference
C-type Natriuretic Peptide (CNP)	Promotes diuresis and natriuresis. Involved in regulation of blood pressure and salt/water/electrolyte	Natriuesis is determined by measuring the amount of sodium in the urine. Diuresis is determined by measuring the amount of urine secreted.	Treatment of Congestive Heart Failure; Hypertension; Cardiovascular disease; Acute tubular necrosis; Acute renal failure; Renal disease; Renal Glomerular disease.	3892, 3893.	See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol

Table 1

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Construct ID	Therapeutic Protein:Z
	balance in body fluids.				2003; 285:F167-177 which is hereby incorporated by reference
Dendroaspis natriuretic peptide (DNP)	Inhibits Na^{+}-K^{+}-ATPase; enhances synthesis of prostaglandin E2 that regulates contraction and relaxation of smooth muscle, as well as the dilation and constriction of blood vessels; inhibits aldosterone secretion; causes diuresis and natriuresis. Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids; renoprotection.	Renal Na^{+}-K^{+}-ATPase activity can be measured using assays known in the art, such as in Ku et al., 1987; Endocrinology 120:2166-2173. Vasodilation can be measured using assays known in the art (Ashton et al. Pharmacology 2000; 61(2):101-105. Prostaglandin E2 synthesis can be determined using assays known in the art, (Cheng et al., J Endocrinol. 2004 Aug;182(2):249-56). Aldosterone levels can be measured using methods known in the art, for example, in Yamato et al., Circ J 2003 May; 67(5):384-90. Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., Ultrasound Med Biol 2003 Mar; 29(3):379-85. Natriuesis is determined by measuring the amount of sodium in the urine. Diuresis is determined by measuring the amount of urine secreted.	Treatment of Congestive Heart Failure; Hypertension; Cardiovascular disease; Acute renal failure; Acute tubular necrosis; Renal disease; Renal Glomerular disease; Cardiac volume overload; cardiac decompensation; Left Ventricular Dysfunction; Dyspnea. Treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiac failure; myocardial reperfusion injury; left ventricle remodeling.	3894, 3895.	See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol 2003; 285:F167-177 which is hereby incorporated by reference
TweakR (Fn 14; Fibroblast growth factor-inducible 14)	Stimulates apoptotic cell death; induces angiogenesis; promotes migration and proliferation of endothelial cells; when mutated causes susceptibility to Klippel-Trenaunay syndrome.	Apoptotic cell death can be measured using assays known in the art, for example, in Nakayama et al., J Immunol. 2003 Jan 1;170(1):341-8). Endothelial cell migration and proliferation can be determined using methods known in the art, for example, in Woods et al., J Biol Chem. 2002 Jan 18;277(3):1924-7.	Treatment of Klippel-Trenaunay syndrome; Cancer; Solid Tumors; Pancreatic Cancer; Colon Cancer; Liver Cancer; Brain Cancer; Gastric Cancer; Lung Cancer; Breast Cancer; Bone Cancer; Autoimmune diseases; Autoimmune disorders; Lupus; Rheumatoid arthritis; Multiple sclerosis; Angiogenesis disorders; Cardiovascular disease.	3919, 3932.	SEQ ID NO:Z for particular construct.
Kiss-1 (Metastin; kisspeptin-54)	Suppresses tumor metastasis; activates G protein-coupled receptor GPR54 to inhibit tumor progression; controls gonadotropin secretion	Activation of GPR54 can be determined using assays known in the art, for example, in Becker et al., Biochem Biophys Res Commun. 2005 Jan 21;326(3):677-86. Gonadotropin secretion can be determined by measuring the amount of gonadotropin hormones in the serum.	Treatment of Cancer; Gastric Carcinomas; Breast Carcinomas; Esophageal Squamous Cell Carcinomas; Bladder Cancer; Solid Tumors; Thyroid Cancer; Pancreatic Cancer; Colon Cancer; Liver Cancer; Lung Cancer; Brain Cancer; Bone Cancer; Gonadotropin deficiency; infertility; Hypopituitarism; Panhypopituitarism; Oligomenorrhea; Amenorrhea; loss of libido; hot flashes; Dyspareunia; impotence; Osteopenia; Hypogonadotropic hypogonadism; Kallmann syndrome; Secondary hypogonadism.	3928; 3929.	See Table 2, SEQ ID NO:Z for particular construct. Also see, Dhar et al., Int J Cancer. 2004 Oct 10;111(6):868-72, Harms et al., Clin Exp Metastasis. 2003;20(1):11-8, or Gottsch et al., Endocrinology. 2004 Sep;145(9):4073-7 which are hereby incorporated by reference
Ephrin B1	Regulates tumor growth and	Tumor growth , angiogenesis, migration and	Cancer; Solid Tumors; Pancreatic Cancer; Colon	3930; 3931;	SEQ ID NO:Z for

Table 1

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Construct ID	Therapeutic Protein:Z
(EFNB1)	angiogenesis; regulates migration and invasion of cancer cells; enhances platelet aggregation and clot maturation; Stimulates T-cell proliferation, lymphokine production, and CTL activity; Stimulates endothelial cell migration and proliferation; required for normal cochlear function	invasion can be measured using assays known in the art (Nakada et al., Cancer Res. 2004 May 1;64(9):3179-85 or Noren et al., Proc Natl Acad Sci U S A. 2004 Apr 13;101(15):5583-8). T-cell proliferation, lymphokine production, and CTL activity can be determined using assays known in the art, for example, in Yu et al., J Biol. Chem. 2004; 279(53):55531-55539. Endothelial cell migration and proliferation can be determined using methods known in the art, for example, in Woods et al., J Biol Chem. 2002 Jan 18;277(3):1924-7. Cochlear function can be determined using assays known in the art (Howard et al., Hear Res. 2003 Apr;178(1-2):118-30).	Cancer; Liver Cancer; Brain Cancer; Colorectal Cancer; Gastric Cancer; Lung Cancer; Bone Cancer; Breast Cancer; Cardiovascular Disease; Hepatocellular carcinoma; T-lymphomas; Graft-versus-host disease (GVH); Autoimmune diseases; Autoimmune disorders; Hemophilia; von Willebrand's disease; Bleeding disorders; Bleeding disorders resulting from Connective tissue disorders; Leukemia; Myeloma; Heart/lung bypass; Kidney dialysis; or drug-induced; Angiogenesis disorders; Cochlear disorders; Hearing loss; Vertigo; Tinnitus; Aural fullness; Acute and/or chronic inner ear disorders.	3934; 3935.	particular construct.
B7-H3	Enhances tumor immunity; Regulates T-Cell activation and immune responses	Tumor immunity can be measured by methods known in the art, for example, in Luo et al., J Immunol. 2004 Nov 1;173(9):5445-50. T-cell activation can be measured using assays known in the art (Chapoval et al., Nat Immunol. 2001 Mar;2(3):269-74).	Cancer; Solid Tumors; Pancreatic Cancer; Colon Cancer; Liver Cancer; Lung Cancer; Bone Cancer; Breast Cancer; Brain Cancer.; Autoimmune disease, Autoimmune Disorders; Osteolytic bone diseases; Hypercalcemia of malignancy; Malignancy-induced bone pain.	3933.	SEQ ID NO:Z for particular construct.

Table 2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
1	3422	pSAC35:APsp.HSA.IFNa	Acid Phosphatase signal peptide followed by mature HSA and IFNa.	pSAC35	149	117	181	213	214	Acid phoshpatase
2	3423	pSAC35:INVsp.HSA.IFNa	Invertase signal peptid followed by mature HSA and IFNa.	pSAC35	150	118	182	215	216	Invertase
3	3424	pSAC35:KTsp.HSA.IFNa	Killer Toxin signal peptide followed by mature HSA and IFNa.	pSAC35	151	119	183	217	218	Killer toxin
4	2249	pSAC35:IFNa2-HSA also named: pSAC23:IFNα2-HSA	Mature IFNa2 fused upstream of mature HSA and downstream of HSA/kex2 leader sequence.	pSAC35	152	120	184	219	220	HSA/kex2
5	2343	pSAC35.INV-IFNA2.HSA	Mature Interferon alpha2 fused upstream of mature HSA and downstream of invertase signal peptide.	pSAC35	153	121	185	221	222	invertase
6	2366	pSAC35.MAF-IFNa2.HSA	Mature IFNa2 fused upstream of mature HSA and downstream of yeast mating factor alpha leader sequence.	pSAC35	154	122	186	223	224	MFα-1
7	2381	pC4:HSA-IFNa2(C17-E181)	Amino acids C17 to E181 of IFNa2 (fragment shown as amino acids C1 to E165 of SEQ ID NO:618) fused downstream of HSA.	pC4	155	123	187	225	226	HSA

Table 2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
8	2382	pC4:IFNa2-HSA	IFNa2 fused upstream of mature HSA.	pC4	156	124	188	227	228	Native IFNα2 leader
9	2410	pSAC35INV:IFNa-HSA	Mature IFNa2 fused downstream of the invertase signal peptide and upstream of mature HSA.	pSAC35	157	125	189	229	230	invertase
10	3165	pSAC35:HSA.IFNa also named CID 3165, pSAC35:HSA.INFa	HSA fused upstream of IFNα and downstream of the HSA/kex2 leader.	pSAC35	158	126	190			HSA/kex2
11	1778	pSAC35:IFNbeta.M22-N187:HSA	Residues M22-N187 of full-length IFNb (shown as M1 to N166 of SEQ ID NO:463) fused upstream of mature HSA and downstream of HSA/kex2 leader sequence.	pSAC35	159	127	191	231	232	HSA/kex2
12	1779	pSAC35:HSA:IFNbeta.M22-N187	Residues M22-N187 of full-length IFNb (shown as M1 to N166 of SEQ ID NO:464) fused downstream of HSA with HSA/kex2 leader sequence.	pSAC35	160	128	192			HSA/kex2
13	2011	pC4:IFNb-HSA	Full length IFNb fused upstream of mature HSA.	pC4	161	129	193	233	234	Native IFNb leader
14	2013	pC4:HSA-IFNb.M22-N187	Amino acids M22 to N187 of IFNb (fragment shown as amino acids M1 to N166 of SEQ ID NO:527) fused downstream of HSA.	pC4	162	130	194			HSA
15	2053	pEE12:IFNb-HSA also named pEE12.1:IFNbeta-HSA	Full length IFNb fused upstream of mature HSA.	pEE12.1	163	131	195			Native IFNb leader
16	2054	pEE12:HSA-IFNb	Mature IFNb fused downstream of HSA.	pEE12.1	164	132	196			HSA
17	2492	pC4.IFNb(deltaM22).HSA	Mutant full length INFbeta fused upstream of mature HSA. First residue of native, mature IFNbeta (M22) has been deleted.	pC4	165	133	197			Native IFNβ leader
18	2580	pC4.IFNb(deltaM22,C38S).HSA	IFNb fused upstream of mature HSA. The IFNb used in this fusion lacks the first residue of the mature form of IFNb, which corresponds to M22 of SEQ ID NO:1687. Also amino acid 38 of SEQ ID NO:1687 has been mutated from Cys to Ser.	pC4	166	134	198			Native IFNβ
19	2795	pC4:HSA(A14)-IFNb.M22-N187	The mature form of IFNb is fused to the C-terminus of HSA, which contains an modified signal peptide, designed to improve processing and homogeneity.	pC4	167	135	199			Modified HSA (A14)
20	2796	pC4:HSA(S14)-IFNb.M22-N187	The mature form of IFNb is fused to the C-terminus of HSA, which contains a modified signal peptide, designed to improve processing and homogeneity.	pC4	168	136	200			Modified HSA (S14)
21	2797	pC4:HSA(G14)-IFNb.M22-N187	The mature form of IFNb is fused to the C-terminus of HSA, which contains an modified signal peptide.	pC4	169	137	201			Modified HSA (G14)
22	2872	pSAC35:HSA.IFNaA(C1-Q91)/D(L93-E166)	This construct contains a hybrid form of IFNaA and IFNaD fused downstream of mature HSA.	pSAC35	170	138	202	235	236	HSA/kex2
23	2873	pSAC35:HSA.IFNaA(C1-Q91)/B(L93-E166)	This construct contains a hybrid form of IFNaA and IFNaB fused downstream of mature HSA.	pSAC35	171	139	203	237	238	HSA/kex2
24	2874	pSAC35:HSA.IFNaA(C1-Q91)/F(L93-E166)	This construct contains a hybrid form of IFNaA and IFNaF fused downstream of mature HSA.	pSAC35	172	140	204	239	240	HSA/kex2

Table 2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
25	2875	pSAC35:HSA.IFNaA(C1Q-62)/D(Q64-E166)	This construct contains a hybrid form of IFNaA and IFNaD fused downstream of mature HSA.	pSAC35	173	141	205	241	242	HSA/kex2
26	2876	pSAC35:HSA.IFNaA(C1-Q91)/D(L93-E166); R23K,A113V	This construct contains a hybrid form of IFNaA and IFNaD fused downstream of mature HSA.	pSAC35	174	142	206	243	244	HSA/kex2
27	1757	pSAC35:IL2.A21-T153.145C/S.HSA	Mature human IL-2 with a single amino acid mutation (C to S at position 145) cloned downstream of the HSA/KEX2 leader and upstream of mature HSA	pSAC35	175	143	207			HSA/kex2
28	1758	pSAC35:HSA.IL2.A21-T153.145C/S	Mature human IL-2 with a single amino acid mutation (C to S at position 145) cloned downstream of HSA with HSA/kex2 leader sequence.	pSAC35	176	144	208			HSA/kex2
29	1812	pSAC35:IL2.A21-T153.HSA	Amino acids A21 to T153 of IL-2 fused downstream of the HSA/kex2 leader and upstream of mature HSA.	pSAC35	177	145	209			HSA/kex2
30	1813	pSAC35:HSA.IL2.A21-T153	Amino acids A21 to T153 of IL-2 fused downstream of HSA with HSA/kex2 leader sequence.	pSAC35	178	146	210			HSA/kex2
31	1952	pcDNA3.1:IL2.HSA	Full length human IL-2, having a Cysteine to Serine mutation at amino acid 145, fused upstream of mature HSA.	pCDNA3.1	179	147	211			Native IL-2 leader
32	1954	pC4:IL2.HSA	Full length human IL-2, having a Cysteine to Serine mutation at amino acid 145, fused upstream of mature HSA.	pC4	180	148	212			Native IL-2 leader
33	3468	pSAC35:KTsp.HSA.GH	Killer toxin signal peptide followed by mature HSA followed by growth hormone.	pSAC35	313	245	381	449	450	Kill toxin PrePro
34	3469	pSAC35:INVsp.HSA.GH	Invertase signal peptide followed by mature HSA followed by growth hormone.	pSAC35	314	246	382	451	452	Invertase
35	3470	pSAC35:APsp.HSA.GH	Acid phosphatase signal peptide followed by mature HSA followed by growth hormone.	pSAC35	315	247	383	453	454	Acid Phosphatase
36	3475	pSAC35:G19Rsp.HSA.GH	Modified HSA/Kex2 signal sequence followed by mature HSA followed by growth hormone	pSAC35	316	248	384	455	456	Modified HSA/Kex2
37	3476	pSAC35:G19Rsp.HSA.IFNa	The Modified HSA/kex2 signal sequence followed by mature HSA followed by INF-alpha.	pSAC35	317	249	385	457	458	Modified HSA/Kex2
38	3549	pSAC35:HSA/kex2.BDNFc.HSA	The HSA/kex2 leader followed by mature BDNFc (splice variant 6) followed by mature HSA.	pSAC35	318	250	386	None	None	HSA/Kex2
39	3610	pSAC35:(HSA/KEX(R19G))SP.GLP-1(7-36A8G)x2.HSA	Modified HSA/kex2 leader followed by yeast codon optimized glp-1 dimer (where the second dimer has been altered so that the wobble position of each codon is different from the first dimer) fused to the N terminus of HSA.	pSAC35	319	251	387	459	460	*Modified* HSA/Kex2
40	3690	pC4:MPIFSP.BNP/HSA	Myeloid progenitor inhibitory factor-1 (MPIF) signal sequence followed by BNP fused to the N-terminus of mature HSA.	pC4	320	252	388	461	462	MPIF-1
41	3691	pC4:SPCON.BNP/HSA	A consensus signal sequence followed by BNP fused to the N-terminus of mature HSA.	pC4	321	253	389	463	464	Consensus
42	3696	pEE12.1:GLP-1(7-36(A8G)x2.HSA	Myeloid progenitor inhibitory factor-1 (MPIF) signal sequence followed by yeast codon optimized glp-1 dimer (where the second dimer has been altered so that the wobble position of each codon is different from the first dimer) fused to the N-terminus of HSA.	pEE12.1	322	254	390	465	466	MPIF-1

Table 2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
43	3715	pSAC35:BNP29/HSA.S65	A single copy of human BNP (amino acids 1-29) fused to the N-terminus of HSA (S65-L585), an HSA N-terminal truncation (delta 1-64). This is downstream of the HSA/Kex2 signal sequence.	pSAC35	323	255	391	467	468	HSA/Kex2
44	3723	pEE12.1:MPIFSP.BNP/HSA	Myeloid progenitor inhibitory factor-1 (MPIF) signal sequence followed by BNP fused to the N-terminus of mature HSA.	pEE12.1	324	256	392	None	None	MPIF-1
45	3724	pEE12.1:SPCON.BNP/HSA	A consensus signal sequence followed by BNP fused to the N-terminus of mature HSA.	pEE12.1	325	257	393	None	None	Consensus
46	3725	pEE12.1:SPCON2.BNP/HSA	A consensus signal sequence followed by BNP fused to the N-terminus of mature HSA.	pEE12.1	326	258	394	None	None	Consensus Signal Peptide #2
47	3736	pC4:SPCON2.BNP/HSA	A consensus signal sequence followed by BNP fused to the N-terminus of mature HSA.	pC4	327	259	395	469	470	Consensus Signal Peptide #2
48	3769	pC4:BNP(R13G)/HSA	Myeloid progenitor inhibitory factor-1 (MPIF) signal sequence followed by BNP mutant (R13G) fused to the N-terminus of mature HSA.	pC4	328	260	396	471	472	MPIF-1
49	3778	pC4:SPCON.BNP29/HSA.S65	A single copy of human BNP (1-29) fused to the N-terminus of HSA (S65-L585), an HSA N-terminal truncation (delta 1-64). This is downstream of a consensus signal sequence.	pC4	329	261	397	473	474	Consensus
50	3783	pC4:SPCON.BNP(R13G)/HSA	Consensus signal sequence followed by BNP mutant (R13G) fused to the N-terminus of mature HSA.	pC4	330	262	398	475	476	Consensus
51	3795	pC4:SPCON.BNP(K14G)/HSA	Consensus signal sequence followed by BNP mutant (K14G) fused to the N-terminus of mature HSA.	pC4	331	263	399	477	478	Consensus
52	3796	pSAC35:HSA/BNP	Followed by mature HSA fused to the N-terminus of BNP.	pSAC35	332	264	400	479	480	HSA/Kex2
53	3809	pSAC35:BNP30(GGG)/HSA	HSA/Kex2 signal sequence followed by BNP (amino acids 1-30) fused via tripartite glycines to the N-terminus of mature HSA.	pSAC35	333	265	401	481	482	HSA/Kex2
54	3886	pSAC35:HSA/KEX2.LANP.HSA	HSA/Kex2 signal sequence followed by LANP fused to the N-terminus of mature HSA. LANP corresponds to amino acids 26-55 of SeqID No:402 (hereby referred to as LANP).	pSAC35	334	266	402	None	None	HSA/Kex2
55	3887	pSAC35:HSA/KEX2.HSA.LANP	HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature LANP.	pSAC35	335	267	403	None	None	HSA/Kex2
56	3888	pSAC35:HSA/KEX2.VDP.HSA	HSA/Kex2 signal sequence followed by VDP fused to the N-terminus of mature HSA. VDP corresponds to amino acids 56-92 of SeqID No:404 (hereby referred to as VDP).	pSAC35	336	268	404	None	None	HSA/Kex2
57	3889	pSAC35:HSA/KEX2.HSA.VDP	HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature VDP.	pSAC35	337	269	405	None	None	HSA/Kex2
58	3890	pSAC35:HSA/KEX2.KUP.HSA	HSA/Kex2 signal sequence followed by KUP fused to the N-terminus of mature HSA. KUP corresponds to amino acids 104-123 of SeqID No:406 (hereby referred to as KUP).	pSAC35	338	270	406	None	None	HSA/Kex2
59	3891	pSAC35:HSA/KEX2.HSA.KUP	HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature KUP.	pSAC35	339	271	407	None	None	HSA/Kex2

Table 2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
60	3892	pSAC35:HSA/KEX2.CNP.HSA	HSA/Kex2 signal sequence followed by CNP fused to the N-terminus of mature HSA. CNP corresponds to amino acids 105-123 of SeqID No:408 (hereby referred to as KUP).	pSAC35	340	272	408	None	None	HSA/Kex2.
61	3893	pSAC35:HSA/KEX2.HSA.CNP	HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature CNP.	pSAC35	341	273	409	None	None	HSA/Kex2
62	3894	pSAC35:HSA/KEX2.DNP.HSA	HSA/Kex2 signal sequence followed by DNP fused to the N-terminus of mature HSA.	pSAC35	342	274	410	None	None	HSA/Kex2
63	3895	pSAC35:HSA/KEX2.HSA.DNP	HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature DNP.	pSAC35	343	275	411	None	None	HSA/Kex2
64	3896	pSAC35:HSA/KEX(R19G)-BNP30(GGG).HSA	Modified HSA/KEX-2 leader followed by BNP (amino acids 1-30) fused via tripartite glycine linker to the N-terminus of mature HSA.	pSAC35	344	276	412	None	None	Modified HSA/Kex2
65	3897	pEE12:SPCON-BNP(K14G).HSA	A consensus signal sequence followed by mutant BNP (K14G) fused to the N-terminus of mature HSA.	pEE12.1	345	277	413	None	None	Consensus
66	3898	pSAC35:HSA/Kex-2-BNP(K14G).HSA	HSA/KEX-2 signal sequence followed by mutant BNP (K14G) fused to the N-terminus of mature HSA.	pSAC35	346	278	414	None	None	HSA/Kex2
67	3899	pSAC35:HSA/Kex-2(R19G)-BNP(K14G).HSA	Modified HSA/KEX-2 signal sequence followed by mutant BNP (K14G) fused to the N-terminus of mature HSA.	pSAC35	347	279	415	None	None	Modified HSA/Kex2
68	3900	pSAC35:HSA/Kex-2-HSA.BNP(K14G)	HSA/KEX-2 signal sequence followed by mature HSA fused to the N-terminus of mutant BNP (K14G).	pSAC35	348	280	416	None	None	HSA/Kex2
69	3903	pC4:SPCON-Uricase.HSA	A consensus signal sequence followed by uricase from rat fused to the N-terminus of mature HSA.	pC4	349	281	417	None	None	Consensus
70	3904	pC4:HSA/Kex2-HSA.Uricase	HSA/KEX-2 signal sequence followed by mature HSA fused to the N-terminus of uricase from rat.	pC4	350	282	418	None	None	HSA/Kex2
71	3910	pSAC35:HSA/Kex-2-ADI.HSA	HSA/KEX-2 signal sequence followed by arginine deiminase from mycoplasma fused to the N-terminus of mature HSA.	pSAC35	351	283	419	None	None	HSA/Kex2
72	3915	pC4:SPCON-ADI.HSA	A consensus signal sequence followed by arginine deiminase from mycoplasma fused to the N-terminus of mature HSA.	pC4	352	284	420	None	None	Consensus
73	3917	pC4:HSA/Kex-2-HSA.ADI	HSA/KEX-2 signal sequence followed by mature HSA fused to the N-terminus of arginine deiminase from mycoplasma.	pC4	353	285	421	None	None	HSA/Kex2
74	3918	pSAC35:HSA/Kex2-HSA.ADI	HSA/KEX-2 signal sequence followed by mature HSA fused to the N-terminus of arginine deiminase from mycoplasma.	pSAC35	354	286	422	None	None	HSA/Kex2
75	3919	pSAC35:KEX2.TWEAKR.E28-F75.HSA	HSA/KEX-2 signal sequence followed by TweakR (amino acids 28-75) fused to the N-terminus of mature HSA. TweakR E28-F75 corresponds to amino acids 28-75 of SeqID No:423 (hereby referred to as TweakR E28-F75).	pSAC35	355	287	423	None	None	HSA/Kex2
76	3920	pSAC35:HSA/Kex2-GCB.HSA	HSA/KEX-2 signal sequence followed by lysosomal glucocerebrosidase fused to the N-terminus of mature HSA.	pSAC35	356	288	424	None	None	HSA/Kex2
77	3921	pC4:SPCON-GCB.HSA	A consensus signal sequence followed by lysosomal glucocerebrosidase fused to the N-terminus of mature HSA.	pC4	357	289	425	None	None	Consensus
78	3922	pSAC35:HSA/Kex2-HSA.GCB	HSA/KEX-2 signal sequence followed by mature HSA fused to the N-terminus of lysosomal glucocerebrosidase.	pSAC35	358	290	426	None	None	HSA/Kex2

Table 2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
79	3923	pC4:HSA/Kex2-HSA.GCB	HSA/KEX-2 signal sequence followed by mature HSA fused to the N-terminus of lysosomal glucocerebrosidase.	pC4	359	291	427	None	None	HSA/Kex2
80	3924	pSAC35:HSA/Kex2-ADM.HSA	HSA/KEX-2 signal sequence followed by adrenomedullin fused to the N-terminus of mature HSA.	pSAC35	360	292	428	None	None	HSA/Kex2
81	3925	pC4:SPCON-ADM.HSA	A consensus signal sequence followed by adrenomedullin fused to the N-terminus of mature HSA.	pC4	361	293	429	None	None	Consensus
82	3926	pSAC35:HSA/Kex2-HSA.ADM	HSA/KEX-2 signal sequence followed by mature HSA fused to the N-terminus of adrenomedullin.	pSAC35	362	294	430	None	None	HSA/Kex2
83	3927	pC4:HSA/Kex2-HSA.ADM	HSA/KEX-2 signal sequence followed by mature HSA fused to the N-terminus of adrenomedullin.	pC4	363	295	431	None	None	HSA/Kex2
84	3928	pc4:HSA.Kiss.E20-Q145	The Pre-pro-region of the HSA signal sequence followed by mature HSA fused to the N-terminus of Kiss (amino acids 20-145). Kiss E20-Q145 corresponds to amino acids 20-145 of SeqID No:432 (hereby referred to as Kiss E20-Q145).	pC4	364	296	432	None	None	HSA Pre-Pro
85	3929	pSAC35:KEX2.HSA.KISS-1.E20-Q145	HSA/KEX-2 signal sequence followed by mature HSA fused to the N-terminus of Kiss (amino acids 20-145).	pSAC35	365	297	433	None	None	HSA/Kex2
86	3930	pSAC35:KEX2.EphrinB1.K30-D229.HSA	HSA/KEX-2 signal sequence followed by Ephrin B1 (amino acids 30-229) fused to the N-terminus of mature HSA. Ephrin B1 K30-D229 corresponds to amino acids 30-229 of SeqID No:434 (hereby referred to as Ephrin B1 K30-D229).	pSAC35	366	298	434	None	None	HSA/Kex2
87	3931	pc4:EphrinB1.M1-D229.HSA	Ephrin B1 (amino acids 1-229), including the native Ephrin B1 signal sequence, fused to the N-terminus of mature HSA.	pC4	367	299	435	None	None	Native Ephrin B1
88	3932	pc4:TWEAKR.M1-F75.HSA	TweakR (amino acids 1-75), including the native TweakR signal sequence, fused to the N-terminus of mature HSA. TweakR M1-F75 corresponds to amino acids 1-75 of SeqID No:436 (hereby referred to as TweakR M1-F75).	pC4	368	300	436	None	None	Native TweakR
89	3933	pc4:B7-H3.M1-E247.HSA	B7-H3 (amino acids 1-247), including the native B7-H3 signal sequence, fused to the N-terminus of mature HSA.	pC4	369	301	437	None	None	Native B7-H3
90	3934	pc4:HSA.EphrinB1.K30-D229	The pre-pro-region of the HSA signal sequence followed by mature HSA fused to the N-terminus of Ephrin B1 (amino acids 30-229).	pC4	370	302	438	None	None	HSA Pre-Pro
91	3935	pSAC35:HSA.EphrinB1.K30-D229	HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of Ephrin B1 (amino acids 30-229).	pSAC35	371	303	439	None	None	HSA/Kex2
92	3936	pc4:SPCON.cUricase.HSA	A consensus signal sequence followed by uricase from chimpanze fused to the N-terminus of mature HSA.	pC4	372	304	440	None	None	Consensus
93	3937	pc4:HSA.cUricase	The pre-pro-region of the HSA signal sequence followed by mature HSA fused to the N-terminus of uricase from chimpanzee.	pC4	373	305	441	None	None	HSA Pre-Pro
94	3938	pc4:SPCON.hUricase.HSA	A consensus signal sequence followed by uricase fused to the N-terminus of mature HSA.	pC4	374	306	442	None	None	Consensus
95	3939	pc4:HSA.hUricase	The pre-pro-region of the HSA signal sequence followed by mature HSA fused to the N-terminus of uricase.	pC4	375	307	443	None	None	HSA Pre-Pro
96	3940	pc4:SPCON.bUricase.HSA	A consensus signal sequence followed by uricase from baboon fused to the N-terminus of mature HSA.	pC4	376	308	444	None	None	Consensus

Table 2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
97	3941	pc4:HSA.bUricase	The pre-pro-region of the HSA signal sequence followed by mature HSA fused to the N-terminus of uricase from baboon.	pC4	377	309	445	None	None	HSA Pre-Pro
98	3942	pSAC35:KEX2.hUricase.HSA	HSA/Kex2 signal sequence followed by uricase fused to the N-terminus of mature HSA.	pSAC35	378	310	446	None	None	HSA/Kex2
99	3943	pSAC35:KEX2.cUricase.HSA	HSA/Kex2 signal sequence followed by uricase from chimpanzee fused to the N-terminus of mature HSA.	pSAC35	379	311	447	None	None	HSA/Kex2
100	3944	pSAC35:KEX2.bUricase.HSA	HSA/Kex2 signal sequence followed by uricase from baboon fused to the N-terminus of mature HSA.	pSAC35	380	312	448	None	None	HSA/Kex2
101	3618	pC4:SPCON.BNP1-32(2x)/HSA	A consensus signal sequence followed by two, tandem copies of mature BNP fused to the N-terminus of mature HSA.	pC4	483	484	485	463	464	Consensus

[0064] Table 2 provides a non-exhaustive list of polynucleotides of the invention comprising, or alternatively consisting of, nucleic acid molecules encoding an albumin fusion protein. The first column, "Fusion No." gives a fusion number to each polynucleotide. Column 2, "Construct ID" provides a unique numerical identifier for each polynucleotide of the invention. The Construct IDs may be used to identify polynucleotides which encode albumin fusion proteins comprising, or alternatively consisting of, a Therapeutic protein portion corresponding to a given Therapeutic Protein:X listed in the corresponding row of Table 1 wherein that Construct ID is listed in column 5. The "Construct Name" column (column 3) provides the name of a given albumin fusion construct or polynucleotide.

[0065] The fourth column in Table 2, "Description" provides a general description of a given albumin fusion construct, and the fifth column, "Expression Vector" lists the vector into which a polynucleotide comprising, or alternatively consisting of, a nucleic acid molecule encoding a given albumin fusion protein was cloned. Vectors are known in the art, and are available commercially or described elsewhere. For example, as described in the Examples, an "expression cassette" comprising, or alternatively consisting of, one or more of (1) a polynucleotide encoding a given albumin fusion protein, (2) a leader sequence, (3) a promoter region, and (4) a transcriptional terminator, may be assembled in a convenient cloning vector and subsequently be moved into an alternative vector, such as, for example, an expression vector including, for example, a yeast expression vector or a mammalian expression vector. In one embodiment, for expression in *S. cervisiae*, an expression cassette comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pSAC35. In another embodiment, for expression in CHO cells, an expression cassette comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pC4. In a further embodiment, a polynucleotide comprising or alternatively consisting of a nucleic acid molecule encoding the Therapeutic protein portion of an albumin fusion protein is cloned into pC4:HSA. In a still further embodiment, for expression in NS0 cells, an expression cassette comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pEE12. Other useful cloning and/or expression vectors will be known to the skilled artisan and are within the scope of the invention.

[0066] Column 6, "SEQ ID NO:Y," provides the full length amino acid sequence of the albumin fusion protein of the invention. In most instances, SEQ ID NO:Y shows the unprocessed form of the albumin fusion protein encoded – in other words, SEQ ID NO:Y shows the signal sequence, a HSA portion, and a therapeutic portion all encoded by the particular construct. Specifically contemplated by the present invention are all polynucleotides that encode SEQ ID NO:Y. When these polynucleotides are used to express the encoded protein from a cell, the cell's natural secretion and processing steps produces a protein that lacks the signal sequence listed in columns 4 and/or 11 of Table 2. The specific amino acid sequence of the listed signal sequence is shown later in the specification or is well known in the art. Thus, most preferred embodiments of the present invention include the albumin fusion protein produced by a cell (which would lack the leader sequence shown in columns 4 and/or 11 of Table 2). Also most preferred are polypeptides comprising SEQ ID NO:Y without the specific leader sequence listed in columns 4 and/or 11 of Table 2. Compositions comprising these two preferred embodiments, including pharmaceutical compositions, are also preferred. Moreover, it is well within the ability of the skilled artisan to replace the signal sequence listed in columns 4 and/or 11 of Table 2 with a different signal sequence, such as those described later in the specification to facilitate secretion of the processed albumin fusion protein.

[0067] The seventh column, "SEQ ID NO:X," provides the parent nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of a given albumin fusion protein may be derived. In one embodiment, the parent nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of an albumin fusion protein may be derived comprises the wild type gene sequence encoding a Therapeutic protein shown in Table 1. In an alternative embodiment, the parent nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of an albumin fusion protein may be derived comprises a variant or derivative of a wild type gene sequence encoding a Therapeutic protein shown in Table 1, such as, for example, a synthetic codon optimized variant of a wild type gene sequence encoding a Therapeutic protein.

[0068] The eighth column, "SEQ ID NO:Z," provides a predicted translation of the parent nucleic acid sequence (SEQ ID NO:X). This parent sequence can be a full length parent protein used to derive the particular construct, the mature portion of a parent protein, a variant or fragment of a wildtype protein, or an artificial sequence that can be used to create the described construct. One of skill in the art can use this amino acid sequence shown in SEQ ID NO:Z to determine which amino acid residues of an albumin fusion protein encoded by a given construct are provided by the therapeutic protein. Moreover, it is well within the ability of the skilled artisan to use the sequence shown as SEQ ID NO:Z to derive the construct described in the same row. For example, if SEQ ID NO:Z corresponds to a full length protein, but only a portion of that protein is used to generate the specific CID, it is within the skill of the art to rely on molecular biology techniques, such as PCR, to amplify the specific fragment and clone it into the appropriate vector.

[0069] Amplification primers provided in columns 9 and 10, "SEQ ID NO:A" and "SEQ ID NO:B" respectively, are exemplary primers used to generate a polynucleotide comprising or alternatively consisting of a nucleic acid molecule encoding the Therapeutic protein portion of a given albumin fusion protein. In one embodiment of the invention, oligonucleotide primers having the sequences shown in columns 9 and/or 10 (SEQ ID NOS:A and/or B) are used to PCR amplify a polynucleotide encoding the Therapeutic protein portion of an albumin fusion protein using a nucleic acid molecule comprising or alternatively consisting of the nucleotide sequence provided in column 7 (SEQ ID NO:X)of the corresponding row as the template DNA. PCR methods are well-established in the art. Additional useful primer sequences could readily be envisioned and utilized by

those of ordinary skill in the art.

[0070] In an alternative embodiment, oligonucleotide primers may be used in overlapping PCR reactions to generate mutations within a template DNA sequence. PCR methods are known in the art.

[0071] As shown in Table 3, certain albumin fusion constructs disclosed in this application have been deposited with the ATCC®.

Table 3

Construct ID	Construct Name	ATCC Deposit No./ Date
1812	pSAC35:IL2.A21-T153.HSA	PTA-3759 Oct. 4, 2001
2053	pEE12:IFNb-HSA also named pEE12.1:IFNβ-HSA	PTA-3764 Oct. 4, 2001
2054	pEE12:HSA-IFNb	PTA-3941 Dec. 19, 2001
2249	pSAC35:IFNa2-HSA also named pSAC23:IFNα2-HSA	PTA-3763 Oct. 4, 2001
2343	pSAC35.INV-IFNA2.HSA	PTA-3940 Dec. 19, 2001
2381	pC4:HSA-IFNa2(C17-E181)	PTA-3942 Dec. 19, 2001
2382	pC4:IFNa2-HSA	PTA-3939 Dec. 19, 2001
2492	pC4.IFNb(deltaM22).HSA	PTA-3943 Dec. 19, 2001
3165	pSAC35:HSA.IFNa also named CID 3165, pSAC35:HSA.INFα	PTA-4670 Sept. 16, 2002

[0072] It is possible to retrieve a given albumin fusion construct from the deposit by techniques known in the art and described elsewhere herein (see, Example 10). The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0073] In a further embodiment of the invention, an "expression cassette" comprising, or alternatively consisting of one or more of (1) a polynucleotide encoding a given albumin fusion protein, (2) a leader sequence, (3) a promoter region, and (4) a transcriptional terminator can be moved or "subcloned" from one vector into another. Fragments to be subcloned may be generated by methods well known in the art, such as, for example, PCR amplification (e.g., using oligonucleotide primers having the sequence shown in SEQ ID NO:A or B), and/or restriction enzyme digestion.

[0074] In preferred embodiments, the albumin fusion proteins of the invention are capable of a therapeutic activity and/or biologic activity corresponding to the therapeutic activity and/or biologic activity of the Therapeutic protein corresponding to the Therapeutic protein portion of the albumin fusion protein listed in the corresponding row of Table 1. In further preferred embodiments, the therapeutically active protein portions of the albumin fusion proteins of the invention are fragments or variants of the protein encoded by the sequence shown in SEQ ID NO:X column of Table 2, and are capable of the therapeutic activity and/or biologic activity of the corresponding Therapeutic protein.

Polypeptide and Polynucleotide Fragments and Variants

Fragments

[0075] The present invention is further directed to fragments of the Therapeutic proteins described in Table 1, albumin proteins, and/or albumin fusion proteins of the invention.

[0076] The present invention is also directed to polynucleotides encoding fragments of the Therapeutic proteins described in Table 1, albumin proteins, and/or albumin fusion proteins of the invention.

[0077] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the Therapeutic protein, albumin protein, and/or albumin fusion protein of the invention, other Therapeutic activities and/or functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of polypeptides with N-terminal deletions to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0078] Accordingly, fragments of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention, include the full length protein as well as polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the reference polypeptide (i.e., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion

protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, N-terminal deletions may be described by the general formula m to q, where q is a whole integer representing the total number of amino acid residues in a reference polypeptide (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein of the invention, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2), and m is defined as any integer ranging from 2 to q minus 6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0079] In addition, fragments of serum albumin polypeptides corresponding to an albumin protein portion of an albumin fusion protein of the invention, include the full length protein as well as polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the reference polypeptide (i.e., serum albumin, or a serum albumin portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In preferred embodiments, N-terminal deletions may be described by the general formula m to 585, where 585 is a whole integer representing the total number of amino acid residues in mature human serum albumin (SEQ ID NO:1), and m is defined as any integer ranging from 2 to 579. Polynucleotides encoding these polypeptides are also encompassed by the invention. In additional embodiments, N-terminal deletions may be described by the general formula m to 609, where 609 is a whole integer representing the total number of amino acid residues in full length human serum albumin (SEQ ID NO:3), and m is defined as any integer ranging from 2 to 603. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0080] Moreover, fragments of albumin fusion proteins of the invention, include the full length albumin fusion protein as well as polypeptides having one or more residues deleted from the amino terminus of the albumin fusion protein (e.g., an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2; or an albumin fusion protein having the amino acid sequence disclosed in column 6 of Table 2). In particular, N-terminal deletions may be described by the general formula m to q, where q is a whole integer representing the total number of amino acid residues in the albumin fusion protein, and m is defined as any integer ranging from 2 to q minus 6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0081] Also as mentioned above, even if deletion of one or more amino acids from the N-terminus or C-terminus of a reference polypeptide (e.g., a Therapeutic protein; serum albumin protein; or albumin fusion protein of the invention) results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) and/or Therapeutic activities may still be retained. For example the ability of polypeptides with C-terminal deletions to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking the N-terminal and/or C-terminal residues of a reference polypeptide retains Therapeutic activity can readily be determined by routine methods described herein and/or otherwise known in the art.

[0082] The present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, C-terminal deletions may be described by the general formula 1 to n, where n is any whole integer ranging from 6 to q minus 1, and where q is a whole integer representing the total number of amino acid residues in a reference polypeptide (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0083] In addition, the present invention provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of an albumin protein corresponding to an albumin protein portion of an albumin fusion protein of the invention (e.g., serum albumin or an albumin protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, C-terminal deletions may be described by the general formula 1 to n, where n is any whole integer ranging from 6 to 584, where 584 is the whole integer representing the total number of amino acid residues in mature human serum albumin (SEQ ID NO:1) minus 1. Polynucleotides encoding these polypeptides are also encompassed by the invention. In particular, C-terminal deletions may be described by the general formula 1 to n, where n is any whole integer ranging from 6 to 608, where 608 is the whole integer representing the total number of amino acid residues in serum albumin (SEQ ID NO:3) minus 1. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0084] Moreover, the present invention provides polypeptides having one or more residues deleted from the carboxy terminus of an albumin fusion protein of the invention. In particular, C-terminal deletions may be described by the general formula 1 to n, where n is any whole integer ranging from 6 to q minus 1, and where q is a whole integer representing the total number of amino acid residues in an albumin fusion protein of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0085] In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted reference polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m to n of a reference polypeptide (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein of the invention, or a Therapeutic protein portion encoded by a polynucleotide or albumin fusion

construct described in Table 2, or serum albumin (e.g., SEQ ID NO:1), or an albumin protein portion of an albumin fusion protein of the invention, or an albumin protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or an albumin fusion protein, or an albumin fusion protein encoded by a polynucleotide or albumin fusion construct of the invention) where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0086] The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a reference polypeptide sequence (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein of the invention, or a Therapeutic protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or serum albumin (e.g., SEQ ID NO: 1), or an albumin protein portion of an albumin fusion protein of the invention, or an albumin protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or an albumin fusion protein, or an albumin fusion protein encoded by a polynucleotide or albumin fusion construct of the invention) set forth herein, or fragments thereof. In preferred embodiments, the application is directed to proteins comprising polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to reference polypeptides having the amino acid sequence of N- and C-terminal deletions as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0087] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a Therapeutic activity and/or functional activity (e.g. biological activity) of the polypeptide sequence of the Therapeutic protein or serum albumin protein of which the amino acid sequence is a fragment.

[0088] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Variants

[0089] "Variant" refers to a polynucleotide or nucleic acid differing from a reference nucleic acid or polypeptide, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the reference nucleic acid or polypeptide.

[0090] As used herein, "variant", refers to a Therapeutic protein portion of an albumin fusion protein of the invention, albumin portion of an albumin fusion protein of the invention, or albumin fusion protein of the invention differing in sequence from a Therapeutic protein (e.g. see "therapeutic" column of Table 1), albumin protein, and/or albumin fusion protein, respectively, but retaining at least one functional and/or therapeutic property thereof as described elsewhere herein or otherwise known in the art. Generally, variants are overall very similar, and, in many regions, identical to the amino acid sequence of the Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein, albumin protein corresponding to an albumin protein portion of an albumin fusion protein, and/or albumin fusion protein. Nucleic acids encoding these variants are also encompassed by the invention.

[0091] The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, the amino acid sequence of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention (e.g., the amino acid sequence of a Therapeutic protein:X disclosed in Table 1; or the amino acid sequence of a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 1 and 2, or fragments or variants thereof), albumin proteins corresponding to an albumin protein portion of an albumin fusion protein of the invention (e.g., the amino acid sequence of an albumin protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 1 and 2; the amino acid sequence shown in SEQ ID NO: 1; or fragments or variants thereof), and/or albumin fusion proteins. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further polypeptides encompassed by the invention are polypeptides encoded by polynucleotides which hybridize to the complement of a nucleic acid molecule encoding an albumin fusion protein of the invention under stringent hybridization conditions (e.g., hybridization to filter bound DNA in 6X Sodium chloride/Sodium citrate (SSC) at about 45 degrees Celsius, followed by one or more washes in 0.2X SSC, 0.1% SDS at about 50 - 65 degrees Celsius), under highly stringent conditions (e.g., hybridization to filter bound DNA in 6X sodium chloride/Sodium citrate (SSC) at about 45 degrees Celsius, followed by one or more washes in 0.1X SSC, 0.2% SDS at about 68 degrees Celsius), or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds., 1989 *Current protocol in Molecular Biology*, Green publishing associates, Inc., and John Wiley & Sons Inc., New York, at pages 6.3.1 - 6.3.6 and 2.10.3). Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0092] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, or substituted with another amino acid. These alterations of the reference sequence may occur at the amino- or carboxy-terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the

reference sequence or in one or more contiguous groups within the reference sequence.

[0093] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of an albumin fusion protein of the invention or a fragment thereof (such as a Therapeutic protein portion of the albumin fusion protein or an albumin portion of the albumin fusion protein), can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[0094] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[0095] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

[0096] The variant will usually have at least 75 % (preferably at least about 80%, 90%, 95% or 99%) sequence identity with a length of normal HA or Therapeutic protein which is the same length as the variant. Homology or identity at the nucleotide or amino acid sequence level is determined by BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx, tblastn and tblastx (Karlin *et al.*, Proc. Natl. Acad. Sci. USA 87: 2264-2268 (1990) and Altschul, J. Mol. Evol. 36: 290-300 (1993), fully incorporated by reference) which are tailored for sequence similarity searching.

[0097] The approach used by the BLAST program is to first consider similar segments between a query sequence and a database sequence, then to evaluate the statistical significance of all matches that are identified and finally to summarize only those matches which satisfy a preselected threshold of significance. For a discussion of basic issues in similarity searching of sequence databases, see Altschul *et al.* (Nature Genetics 6: 119-129 (1994)) which is fully incorporated by reference. The search parameters for histogram, descriptions, alignments, expect (i.e., the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter are at the default settings. The default scoring matrix used by blastp, blastx, tblastn, and tblastx is the BLOSUM62 matrix (Henikoff *et al.*, Proc. Natl. Acad. Sci. USA 89: 10915-10919 (1992), fully incorporated by reference). For blastn, the scoring matrix is set by the ratios of M (i.e., the reward score for a pair of matching residues) to N (i.e., the penalty score for mismatching residues), wherein the default values for M and N are 5 and -4, respectively. Four blastn parameters may be adjusted as follows: Q=10 (gap creation penalty); R=10 (gap extension penalty); wink=1 (generates word hits at every winkth position along the query); and gapw=16 (sets the window width within which gapped alignments are generated). The equivalent Blastp parameter settings were Q=9; R=2; wink=1; and gapw=32. A Bestfit comparison between sequences, available in the GCG package version 10.0, uses DNA parameters GAP=50 (gap creation penalty) and LEN=3 (gap extension penalty) and the equivalent settings in protein comparisons are GAP=8 and LEN=2.

[0098] The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are

preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host, such as, yeast or *E. coli*).

[0099] In a preferred embodiment, a polynucleotide of the invention which encodes the albumin portion of an albumin fusion protein is optimized for expression in yeast or mammalian cells. In a further preferred embodiment, a polynucleotide of the invention which encodes the Therapeutic protein portion of an albumin fusion protein is optimized for expression in yeast or mammalian cells. In a still further preferred embodiment, a polynucleotide encoding an albumin fusion protein of the invention is optimized for expression in yeast or mammalian cells.

[00100] In an alternative embodiment, a codon optimized polynucleotide which encodes a Therapeutic protein portion of an albumin fusion protein does not hybridize to the wild type polynucleotide encoding the Therapeutic protein under stringent hybridization conditions as described herein. In a further embodiment, a codon optimized polynucleotide which encodes an albumin portion of an albumin fusion protein does not hybridize to the wild type polynucleotide encoding the albumin protein under stringent hybridization conditions as described herein. In another embodiment, a codon optimized polynucleotide which encodes an albumin fusion protein does not hybridize to the wild type polynucleotide encoding the Therapeutic protein portion or the albumin protein portion under stringent hybridization conditions as described herein.

[0100] In an additional embodiment, a polynucleotide which encodes a Therapeutic protein portion of an albumin fusion protein does not comprise, or alternatively consist of, the naturally occurring sequence of that Therapeutic protein. In a further embodiment, a polynucleotide which encodes an albumin protein portion of an albumin fusion protein does not comprise, or alternatively consist of, the naturally occurring sequence of albumin protein. In an alternative embodiment, a polynucleotide which encodes an albumin fusion protein does not comprise, or alternatively consist of, the naturally occurring sequence of a Therapeutic protein portion or the albumin protein portion.

[0101] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985)). These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

[0102] Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. As an example, Ron et al. (J. Biol. Chem. 268: 2984-2988 (1993)) reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

[0103] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[0104] Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0105] Thus, the invention further includes polypeptide variants which have a functional activity (e.g., biological activity and/or therapeutic activity). In one embodiment, the invention provides variants of albumin fusion proteins that have a functional activity (e.g., biological activity and/or therapeutic activity) that corresponds to one or more biological and/or therapeutic activities of the Therapeutic protein corresponding to the Therapeutic protein portion of the albumin fusion protein. In another embodiment, the invention provides variants of albumin fusion proteins that have a functional activity (e.g., biological activity and/or therapeutic activity) that corresponds to one or more biological and/or therapeutic activities of the Therapeutic protein corresponding to the Therapeutic protein portion of the albumin fusion protein. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. Polynucleotides encoding such variants are also encompassed by the invention.

[0106] In preferred embodiments, the variants of the invention have conservative substitutions. By "conservative substitutions" is intended swaps within groups such as replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys,

Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

[0107] Guidance concerning how to make phenotypically silent amino acid substitutions is provided, for example, in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[0108] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[0109] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham and Wells, Science 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

[0110] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) polypeptides containing substitutions of one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) polypeptides containing substitutions of one or more of the amino acid residues having a substituent group, or (iii) polypeptides which have been fused with or chemically conjugated to another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), (iv) polypeptide containing additional amino acids, such as, for example, an IgG Fc fusion region peptide. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[0111] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

[0112] In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of the amino acid sequence of an albumin fusion protein, the amino acid sequence of a Therapeutic protein and/or human serum albumin, wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Nucleic acids encoding these polypeptides are also encompassed by the invention.

[0113] The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as post-translational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POST-TRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol.

182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

Functional activity

[0114] "A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with the full-length, pro-protein, and/or mature form of a Therapeutic protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

[0115] "A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a Therapeutic protein of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

[0116] In preferred embodiments, an albumin fusion protein of the invention has at least one biological and/or therapeutic activity associated with the Therapeutic protein portion (or fragment or variant thereof) when it is not fused to albumin.

[0117] In additional preferred embodiments, the albumin fusion protein of the invention has an increased plasma stability compared to the Therapeutic protein portion (or fragment or variant thereof) in an unfused state. Plasma stability of the albumin fusion protein of the invention or of the unfused Therapeutic protein portion (or fragment or variant thereof) can be assayed using or routinely modifying assays known in the art.

[0118] The albumin fusion proteins of the invention can be assayed for functional activity (e.g., biological activity) using or routinely modifying assays known in the art, as well as assays described herein. Additionally, one of skill in the art may routinely assay fragments of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein, for activity using assays referenced in its corresponding row of Table 1 (e.g., in column 3 of Table 1). Further, one of skill in the art may routinely assay fragments of an albumin protein corresponding to an albumin protein portion of an albumin fusion protein, for activity using assays known in the art and/or as described in the Examples section below.

[0119] For example, in one embodiment where one is assaying for the ability of an albumin fusion protein to bind or compete with a Therapeutic protein for binding to an anti-Therapeutic polypeptide antibody and/or anti-albumin antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[0120] In a preferred embodiment, where a binding partner (e.g., a receptor or a ligand) of a Therapeutic protein is identified, binding to that binding partner by an albumin fusion protein which comprises that Therapeutic protein as the Therapeutic protein portion of the fusion can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological correlates of an albumin fusion protein to bind to a substrate(s) of the Therapeutic polypeptide corresponding to the Therapeutic protein portion of the fusion can be routinely assayed using techniques known in the art.

[0121] In an alternative embodiment, where the ability of an albumin fusion protein to multimerize is being evaluated, association with other components of the multimer can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., *supra*.

[0122] In preferred embodiments, an albumin fusion protein comprising all or a portion of an antibody that binds a Therapeutic protein, has at least one biological and/or therapeutic activity (e.g., to specifically bind a polypeptide or epitope) associated with the antibody that binds a Therapeutic protein (or fragment or variant thereof) when it is not fused to albumin. In other preferred embodiments, the biological activity and/or therapeutic activity of an albumin fusion protein comprising all or a portion of an antibody that binds a Therapeutic protein is the inhibition (i.e., antagonism) or activation (i.e., agonism) of one or more of the biological activities and/or therapeutic activities associated with the polypeptide that is specifically bound by antibody that binds a Therapeutic protein.

[0123] Albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be characterized in a variety of ways. In particular, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for the ability to specifically bind to the same antigens specifically bound by the antibody that binds a Therapeutic protein

corresponding to the Therapeutic protein portion of the albumin fusion protein using techniques described herein or routinely modifying techniques known in the art.

[0124] Assays for the ability of the albumin fusion proteins (e.g., comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) to (specifically) bind a specific protein or epitope may be performed in solution (*e.g.*, Houghten, Bio/Techniques 13:412-421(1992)), on beads (*e.g.*, Lam, Nature 354:82-84 (1991)), on chips (*e.g.*, Fodor, Nature 364:555-556 (1993)), on bacteria (*e.g.*, U.S. Patent No. 5,223,409), on spores (*e.g.*, Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (*e.g.*, Cull et al., Proc. Natl. Acad. Sci. USA 89:1865-1869 (1992)) or on phage (*e.g.*, Scott and Smith, Science 249:386-390 (1990); Devlin, Science 249:404-406 (1990); Cwirla et al., Proc. Natl. Acad. Sci. USA 87:6378-6382 (1990); and Felici, J. Mol. Biol. 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). Albumin fusion proteins comprising at least a fragment or variant of a Therapeutic antibody may also be assayed for their specificity and affinity for a specific protein or epitope using or routinely modifying techniques described herein or otherwise known in the art.

[0125] The albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for cross-reactivity with other antigens (e.g., molecules that have sequence/structure conservation with the molecule(s) specifically bound by the antibody that binds a Therapeutic protein (or fragment or variant thereof) corresponding to the Therapeutic protein portion of the albumin fusion protein of the invention) by any method known in the art.

[0126] Immunoassays which can be used to analyze (immunospecific) binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0127] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding the albumin fusion protein of the invention (*e.g.*, comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40 degrees C, adding sepharose beads coupled to an anti-albumin antibody, for example, to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the albumin fusion protein to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the albumin fusion protein to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

[0128] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), applying the albumin fusion protein of the invention (diluted in blocking buffer) to the membrane, washing the membrane in washing buffer, applying a secondary antibody (which recognizes the albumin fusion protein, *e.g.*, an anti-human serum albumin antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, ^{32}P or ^{125}I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

[0129] ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the albumin fusion protein (*e.g.*, comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) of the invention conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound or non-specifically bound albumin fusion proteins, and detecting the presence of the albumin fusion proteins specifically bound to the antigen coating the well. In ELISAs the albumin fusion protein does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes albumin fusion protein) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the albumin fusion protein may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in

Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

[0130] The binding affinity of an albumin fusion protein to a protein, antigen, or epitope and the off-rate of an albumin fusion protein-protein/antigen/epitope interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*, ^{3}H or ^{125}I) with the albumin fusion protein of the invention in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the albumin fusion protein for a specific protein, antigen, or epitope and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second protein that binds the same protein, antigen or epitope as the albumin fusion protein, can also be determined using radioimmunoassays. In this case, the protein, antigen or epitope is incubated with an albumin fusion protein conjugated to a labeled compound (*e.g.*, ^{3}H or ^{125}I) in the presence of increasing amounts of an unlabeled second protein that binds the same protein, antigen, or epitope as the albumin fusion protein of the invention.

[0131] In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of albumin fusion proteins of the invention to a protein, antigen or epitope. BIAcore kinetic analysis comprises analyzing the binding and dissociation of albumin fusion proteins, or specific polypeptides, antigens or epitopes from chips with immobilized specific polypeptides, antigens or epitopes or albumin fusion proteins, respectively, on their surface.

[0132] Antibodies that bind a Therapeutic protein corresponding to the Therapeutic protein portion of an albumin fusion protein may also be described or specified in terms of their binding affinity for a given protein or antigen, preferably the antigen which they specifically bind. Preferred binding affinities include those with a dissociation constant or Kd less than $5 X 10^{-2}$ M, 10^{-2} M, $5 X 10^{-3}$ M, 10^{-3} M, $5 X 10^{-4}$ M, 10^{-4} M. More preferred binding affinities include those with a dissociation constant or Kd less than $5 X 10^{-5}$ M, 10^{-5} M, $5 X 10^{-6}$ M, 10^{-6}M, $5 X 10^{-7}$ M; 10^{7} M, $5 X 10^{-8}$ M or 10^{-8} M. Even more preferred binding affinities include those with a dissociation constant or Kd less than $5 X 10^{-9}$ M, 10^{-9} M, $5 X 10^{-10}$ M, 10^{-10} M, $5 X 10^{-11}$ M, 10^{-11} M, $5 X 10^{-12}$ M, $^{10-12}$ M, $5 X 10^{-13}$ M, 10^{-13} M, $5 X 10^{-14}$ M, 10^{-14} M, $5 X 10^{-15}$ M, or 10^{-15} M. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has an affinity for a given protein or epitope similar to that of the corresponding antibody (not fused to albumin) that binds a Therapeutic protein, taking into account the valency of the albumin fusion protein (comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) and the valency of the corresponding antibody. In addition, assays described herein (see Examples and Table 1) and otherwise known in the art may routinely be applied to measure the ability of albumin fusion proteins and fragments, variants and derivatives thereof to elicit biological activity and/or Therapeutic activity (either *in vitro* or *in vivo*) related to either the Therapeutic protein portion and/or albumin portion of the albumin fusion protein. Other methods will be known to the skilled artisan and are within the scope of the invention.

Albumin

[0133] As described above, an albumin fusion protein of the invention comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion.

[0134] An additional embodiment comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are linked to one another by chemical conjugation.

[0135] The terms, human serum albumin (HSA) and human albumin (HA) are used interchangeably herein. The terms, "albumin and "serum albumin" are broader, and encompass human serum albumin (and fragments and variants thereof) as well as albumin from other species (and fragments and variants thereof).

[0136] As used herein, "albumin" refers collectively to albumin protein or amino acid sequence, or an albumin fragment or variant, having one or more functional activities (e.g., biological activities) of albumin. In particular, "albumin" refers to human albumin or fragments thereof (see for example, EP 201 239, EP 322 094 WO 97/24445, WO95/23857) especially the mature form of human albumin as shown in Figure 1 and SEQ ID NO: 1, or albumin from other vertebrates or fragments thereof, or analogs or variants of these molecules or fragments thereof.

[0137] In preferred embodiments, the human serum albumin protein used in the albumin fusion proteins of the invention contains one or both of the following sets of point mutations with reference to SEQ ID NO: 1: Leu-407 to Ala, Leu-408 to Val, Val-409 to Ala, and Arg-410 to Ala; or Arg-410 to A, Lys-413 to Gln, and Lys-414 to Gln (see, e.g., International Publication No. WO95/23857, hereby incorporated in its entirety by reference herein). In even more preferred embodiments, albumin fusion proteins of the invention that contain one or both of above-described sets of point mutations have improved stability/resistance to yeast Yap3p proteolytic cleavage, allowing increased production of recombinant albumin fusion proteins expressed in yeast host cells.

[0138] As used herein, a portion of albumin sufficient to prolong the therapeutic activity or plasma stability or shelf-life of the Therapeutic protein refers to a portion of albumin sufficient in length or structure to stabilize or prolong the therapeutic activity or plasma stability of the protein so that the shelf life or plasma stability of the Therapeutic protein portion of the albumin fusion protein is prolonged or extended compared to the shelf-life or plasma stability in the non-fusion state. The albumin portion of the albumin fusion proteins may comprise the full length of the HA sequence as described above, or may include one or more fragments thereof that are capable of stabilizing or prolonging the therapeutic activity. Such fragments may be of 10 or more amino acids in length or may include about 15, 20, 25, 30, 50, or more contiguous amino acids from the HA

sequence or may include part or all of specific domains of HA. For instance, one or more fragments of HA spanning the first two immunoglobulin-like domains may be used. In a preferred embodiment, the HA fragment is the mature form of HA.

[0139] The albumin portion of the albumin fusion proteins of the invention may be a variant of normal HA. The Therapeutic protein portion of the albumin fusion proteins of the invention may also be variants of the Therapeutic proteins as described herein. The term "variants" includes insertions, deletions and substitutions, either conservative or non conservative, where such changes do not substantially alter one or more of the oncotic, useful ligand-binding and non-immunogenic properties of albumin, or the active site, or active domain which confers the therapeutic activities of the Therapeutic proteins.

[0140] In particular, the albumin fusion proteins of the invention may include naturally occurring polymorphic variants of human albumin and fragments of human albumin, for example those fragments disclosed in EP 322 094 (namely HA (Pn), where n is 369 to 419). The albumin may be derived from any vertebrate, especially any mammal, for example human, cow, sheep, or pig. Non-mammalian albumins include, but are not limited to, hen and salmon. The albumin portion of the albumin fusion protein may be from a different animal than the Therapeutic protein portion.

[0141] Generally speaking, an HA fragment or variant will be at least 100 amino acids long, preferably at least 150 amino acids long. The HA variant may consist of or alternatively comprise at least one whole domain of HA, for example domains 1 (amino acids 1-194 of SEQ ID NO: 1), domain 2 (amino acids 195-387 of SEQ ID NO:1), domain 3 (amino acids 388-585 of SEQ ID NO:1), domains 1 and 2 (1-387 of SEQ ID NO:1), domains 2 and 3 (195-585 of SEQ ID NO:1) or domains 1 and 3 (amino acids 1-194 of SEQ ID NO:1 and amino acids 388-585 of SEQ ID NO:1). Each domain is itself made up of two homologous subdomains namely 1-105, 120-194, 195-291, 316-387, 388-491 and 512-585, with flexible inter-subdomain linker regions comprising residues Lys106 to Glu119, Glu292 to Val315 and Glu492 to Ala511.

[0142] Preferably, the albumin portion of an albumin fusion protein of the invention comprises at least one subdomain or domain of HA or conservative modifications thereof. If the fusion is based on subdomains, some or all of the adjacent linker is preferably used to link to the Therapeutic protein moiety.

Antibodies that Specifically bind Therapeutic proteins are also Therapeutic proteins

[0143] The present invention also encompasses albumin fusion proteins that comprise at least a fragment or variant of an antibody that specifically binds a Therapeutic protein disclosed in Table 1. It is specifically contemplated that the term "Therapeutic protein" encompasses antibodies that bind a Therapeutic protein (e.g., as Described in column I of Table 1) and fragments and variants thereof. Thus an albumin fusion protein of the invention may contain at least a fragment or variant of a Therapeutic protein, and/or at least a fragment or variant of an antibody that binds a Therapeutic protein.

Antibody structure and background

[0144] The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. *See generally, Fundamental Immunology* Chapters 3-5 (Paul, W., ed., 4th ed. Raven Press, N.Y. (1998)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site.

[0145] Thus, an intact IgG antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are the same.

[0146] The chains all exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDR regions, in general, are the portions of the antibody which make contact with the antigen and determine its specificity. The CDRs from the heavy and the light chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains variable regions comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The variable regions are connected to the heavy or light chain constant region. The assignment of amino acids to each domain is in accordance with the definitions of Kabat *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk J *Mol. Biol.* 196:901-917 (1987); Chothia et al. *Nature* 342:878-883 (1989).

[0147] As used herein, "antibody" refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that specifically binds an antigen (e.g., a molecule containing one or more CDR regions of an antibody). Antibodies that may correspond to a Therapeutic protein portion of an albumin fusion protein include, but are not limited to, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies (e.g., single chain Fvs), Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies specific to antibodies of the invention), and epitope-binding fragments of any of the above (e.g., VH domains, VL domains, or one or more CDR regions).

Antibodies that bind Therapeutic Proteins

[0148] The present invention encompasses albumin fusion proteins that comprise at least a fragment or variant of an antibody that binds a Therapeutic Protein (e.g., as disclosed in Table 1) or fragment or variant thereof.

[0149] Antibodies that bind a Therapeutic protein (or fragment or variant thereof) may be from any animal origin, including birds and mammals. Preferably, the antibodies are human, murine (*e.g.*, mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken antibodies. Most preferably, the antibodies are human antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries and xenomice or other organisms that have been genetically engineered to produce human antibodies.

[0150] The antibody molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the antibody molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are IgG1. In other preferred embodiments, the immunoglobulin molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are IgG2. In other preferred embodiments, the immunoglobulin molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are IgG4.

[0151] Most preferably the antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains.

[0152] The antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a Therapeutic protein or may be specific for both a Therapeutic protein as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[0153] Antibodies that bind a Therapeutic protein (or fragment or variant thereof) may be bispecific or bifunctional which means that the antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. *See, e.g.*, Songsivilai & Lachmann *Clin. Exp. Immunol.* 79: 315-321 (1990), Kostelny et al. J *Immunol.* 148:1547 1553 (1992). In addition, bispecific antibodies may be formed as "diabodies" (Holliger et al. "'Diabodies': small bivalent and bispecific antibody fragments" PNAS USA 90:6444-6448 (1993)) or "Janusins" (Traunecker et al. "Bispecific single chain molecules (Janusins) target cytotoxic lymphocytes on HIV infected cells" *EMBO J* 10:3655-3659 (1991) and Traunecker et al. "Janusin: new molecular design for bispecific reagents" *Int J Cancer Suppl* 7:51-52 (1992)).

[0154] The present invention also provides albumin fusion proteins that comprise, fragments or variants (including derivatives) of an antibody described herein or known elsewhere in the art. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. In specific embodiments, the variants encode substitutions of VHCDR3. In a preferred embodiment, the variants have conservative amino acid substitutions at one or more predicted non-essential amino acid residues.

[0155] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein may be described or specified in terms of the epitope(s) or portion(s) of a Therapeutic protein which they recognize or specifically bind. Antibodies which specifically bind a Therapeutic protein or a specific epitope of a Therapeutic protein may also be excluded. Therefore, the present invention encompasses antibodies that specifically bind Therapeutic proteins, and allows for the exclusion of the same. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, binds the same epitopes as the unfused fragment or variant of that antibody itself.

[0156] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a Therapeutic protein are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% sequence identity (as calculated using methods known in the art and described herein) to a Therapeutic protein are also included in the present invention. In specific embodiments, antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less

than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% sequence identity (as calculated using methods known in the art and described herein) to a Therapeutic protein are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has similar or substantially identical cross reactivity characteristics compared to the fragment or variant of that particular antibody itself.

[0157] Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide encoding a Therapeutic protein under stringent hybridization conditions (as described herein). Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10^{-2} M, 10^{-2} M, 5 X 10^{-3} M, 10^{-3} M, 5 X 10^{-4} M, 10^{-4} M. More preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10^{-5} M, 10^{-5} M, 5 X 10^{-6} M, 10^{-6}M, 5 X 10^{-7} M, 10^{7} M, 5 X 10^{-8} M or 10^{-8} M. Even more preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10^{-9} M, 10^{-9} M, 5 X 10^{-10} M, 10^{-10} M, 5 X 10^{-11} M, 10^{-11} M, 5 X 10^{-12} M, $^{10-12}$ M, 5 X 10^{-13} M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, or 10^{-15} M. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has an affinity for a given protein or epitope similar to that of the corresponding antibody (not fused to albumin) that binds a Therapeutic protein, taking into account the valency of the albumin fusion protein (comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) and the valency of the corresponding antibody.

[0158] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of a Therapeutic protein as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, competitively inhibits binding of a second antibody to an epitope of a Therapeutic protein. In other preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, competitively inhibits binding of a second antibody to an epitope of a Therapeutic protein by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[0159] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may act as agonists or antagonists of the Therapeutic protein. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has similar or substantially similar characteristics with regard to preventing ligand binding and/or preventing receptor activation compared to an un-fused fragment or variant of the antibody that binds the Therapeutic protein.

[0160] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the Therapeutic proteins (e.g. as disclosed in Table 1). The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties). In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, have similar or substantially identical agonist or antagonist properties as an un-fused fragment or variant of the antibody that binds the Therapeutic protein.

[0161] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may be used, for example, to purify, detect, and target Therapeutic proteins, including both in *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the Therapeutic protein in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety. Likewise, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, may be used, for example, to purify, detect, and target Therapeutic proteins, including both *in vitro* and *in vivo* diagnostic and therapeutic methods.

[0162] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids. Albumin fusion proteins of the invention may also be modified as described above.

Methods of Producing Antibodies that bind Therapeutic Proteins

[0163] The antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a Therapeutic protein may be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0164] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0165] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. In a non-limiting example, mice can be immunized with a Therapeutic protein or fragment or variant thereof, an albumin fusion protein, or a cell expressing such a Therapeutic protein or fragment or variant thereof or albumin fusion protein. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0166] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[0167] Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of Current Protocols in Immunology, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

[0168] In general, the sample containing human B cells is innoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g, SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

[0169] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

[0170] For example, antibodies that bind to a Therapeutic protein can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make antibodies that bind to a Therapeutic protein include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0171] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[0172] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[0173] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[0174] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181; and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0175] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

Polynucleotides Encoding Antibodies

[0176] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a Therapeutic protein, and more preferably, an antibody that binds to a polypeptide having the amino acid sequence of a "Therapeutic protein:X" as disclosed in the "SEQ ID NO:Z" column of Table 2.

[0177] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0178] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art (See Example 65).

[0179] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0180] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[0181] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[0182] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Recombinant Expression of Antibodies

[0183] Recombinant expression of an antibody, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody or a single chain antibody), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[0184] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0185] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For

example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

[0186] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0187] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0188] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or *in vivo* recombination. Insertion in a non- essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[0189] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[0190] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

[0191] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215 (1993)); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be

routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

[0192] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

[0193] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al., Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entireties by reference herein.

[0194] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0195] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

Modifications of Antibodies

[0196] Antibodies that bind a Therapeutic protein or fragments or variants can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin tag (also called the "HA tag"), which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[0197] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 131I, 111In or 99Tc. Other examples of detectable substances have been described elsewhere herein.

[0198] Further, an antibody of the invention may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0199] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol., 6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0200] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0201] Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[0202] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0203] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Antibody-albumin fusion

[0204] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention include, but are not limited to, antibodies that bind a Therapeutic protein disclosed in the "Therapeutic Protein X" column of Table 1, or a fragment or variant thereof.

[0205] In specific embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH domain. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, one, two or three VH CDRs. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH CDR1. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH CDR2. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH CDR3.

[0206] In specific embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL domain. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, one, two or three VL CDRs. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an

albumin fusion protein comprises, or alternatively consists of, the VL CDR1. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL CDR2. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL CDR3.

[0207] In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, one, two, three, four, five, or six VH and/or VL CDRs.

[0208] In preferred embodiments, the fragment or variant of an antibody that immunospecifically binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, an scFv comprising the VH domain of the Therapeutic antibody, linked to the VL domain of the therapeutic antibody by a peptide linker such as $(Gly_4Ser)_3$ (SEQ ID NO:4).

Immunophenotyping

[0209] The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) may be utilized for immunophenotyping of cell lines and biological samples. Therapeutic proteins of the present invention may be useful as cell-specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies (or albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies (or albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al., Cell, 96*:737-49 (1999)).

[0210] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Characterizing Antibodies that bind a Therapeutic Protein and Albumin Fusion Proteins Comprising a Fragment or Variant of an Antibody that binds a Therapeutic Protein

[0211] The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) may be characterized in a variety of ways. In particular, Albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for the ability to specifically bind to the same antigens specifically bound by the antibody that binds a Therapeutic protein corresponding to the antibody that binds a Therapeutic protein portion of the albumin fusion protein using techniques described herein or routinely modifying techniques known in the art.

[0212] Assays for the ability of the antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) to (specifically) bind a specific protein or epitope may be performed in solution (*e.g.*, Houghten, Bio/Techniques 13:412-421(1992)), on beads (*e.g.*, Lam, Nature 354:82-84 (1991)), on chips (*e.g.*, Fodor, Nature 364:555-556 (1993)), on bacteria (*e.g.*, U.S. Patent No. 5,223,409), on spores (*e.g.*, Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (*e.g.*, Cull et al., Proc. Natl. Acad. Sci. USA 89:1865-1869 (1992)) or on phage (*e.g.*, Scott and Smith, Science 249:386-390 (1990); Devlin, Science 249:404-406 (1990); Cwirla et al., Proc. Natl. Acad. Sci. USA 87:6378-6382 (1990); and Felici, J. Mol. Biol. 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) may also be assayed for their specificity and affinity for a specific protein or epitope using or routinely modifying techniques described herein or otherwise known in the art.

[0213] The albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for cross-reactivity with other antigens (e.g., molecules that have sequence/structure conservation with the molecule(s) specifically bound by the antibody that binds a Therapeutic protein (or fragment or variant thereof) corresponding to the Therapeutic protein portion of the albumin fusion protein of the invention) by any method known in the art.

[0214] Immunoassays which can be used to analyze (immunospecific) binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below

(but are not intended by way of limitation).

[0215] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding an antibody of the invention or albumin fusion protein of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40 degrees C, adding protein A and/or protein G sepharose beads (or beads coated with an appropriate anti-idiotypic antibody or anti-albumin antibody in the case when an albumin fusion protein comprising at least a fragment or variant of a Therapeutic antibody) to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody or albumin fusion protein of the invention to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody or albumin fusion protein to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

[0216] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), applying the antibody or albumin fusion protein of the invention (diluted in blocking buffer) to the membrane, washing the membrane in washing buffer, applying a secondary antibody (which recognizes the albumin fusion protein, *e.g.*, an anti-human serum albumin antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, ^{32}P or ^{125}I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

[0217] ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody or albumin fusion protein (comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) of the invention conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound or non-specifically bound albumin fusion proteins, and detecting the presence of the antibody or albumin fusion proteins specifically bound to the antigen coating the well. In ELISAs the antibody or albumin fusion protein does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody or albumin fusion protein, respectively) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, antibody or the albumin fusion protein may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

[0218] The binding affinity of an albumin fusion protein to a protein, antigen, or epitope and the off-rate of an antibody- or albumin fusion protein-protein/antigen/epitope interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*, ^{3}H or ^{125}I) with the antibody or albumin fusion protein of the invention in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody or albumin fusion protein of the invention for a specific protein, antigen, or epitope and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second protein that binds the same protein, antigen or epitope as the antibody or albumin fusion protein, can also be determined using radioimmunoassays. In this case, the protein, antigen or epitope is incubated with an antibody or albumin fusion protein of the invention conjugated to a labeled compound (*e.g.*, ^{3}H or ^{125}I) in the presence of increasing amounts of an unlabeled second protein that binds the same protein, antigen, or epitope as the albumin fusion protein of the invention.

[0219] In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibody or albumin fusion proteins of the invention to a protein, antigen or epitope. BIAcore kinetic analysis comprises analyzing the binding and dissociation of antibodies, albumin fusion proteins, or specific polypeptides, antigens or epitopes from chips with immobilized specific polypeptides, antigens or epitopes, antibodies or albumin fusion proteins, respectively, on their surface.

Therapeutic Uses

[0220] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds

of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein), nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein), albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, and nucleic acids encoding such albumin fusion proteins. The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a Therapeutic protein, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a Therapeutic protein includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0221] In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein to an animal, preferably a mammal, and most preferably a human, patient for treating one or more diseases, disorders, or conditions, including but not limited to: neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions., and/or as described elsewhere herein. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a Therapeutic protein and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a Therapeutic protein, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a Therapeutic protein includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0222] A summary of the ways in which the antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be used therapeutically includes binding Therapeutic proteins locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0223] The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0224] The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0225] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against Therapeutic proteins, fragments or regions thereof, (or the albumin fusion protein correlate of such an antibody) for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include dissociation constants or Kd's less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M. More preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6}M, 5×10^{-7} M, 10^{7} M, 5×10^{-8} M or 10^{-8} M. Even more preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

Gene Therapy

[0226] In a specific embodiment, nucleic acids comprising sequences encoding antibodies that bind therapeutic proteins or albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a Therapeutic protein, by way of gene therapy. Gene therapy refers to

therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0227] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described in more detail elsewhere in this application.

Demonstration of Therapeutic or Prophylactic Activity

[0228] The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

[0229] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[0230] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0231] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0232] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0233] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

[0234] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

[0235] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0236] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)),

etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0237] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0238] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0239] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0240] The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a Therapeutic protein can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

[0241] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

Diagnosis and Imaging

[0242] Labeled antibodies and derivatives and analogs thereof that bind a Therapeutic protein (or fragment or variant thereof) (including albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein), can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of Therapeutic protein. The invention provides for the detection of aberrant expression of a Therapeutic protein, comprising (a) assaying the expression of the Therapeutic protein in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed Therapeutic protein expression level compared to the standard expression level is indicative of aberrant expression.

[0243] The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the Therapeutic protein in cells or body fluid of an individual using one or more antibodies specific to the Therapeutic protein or albumin fusion proteins comprising at least a fragment of variant of an antibody specific to a Therapeutic protein, and (b) comparing the level of gene expression with a standard gene expression

level, whereby an increase or decrease in the assayed Therapeutic protein gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0244] Antibodies of the invention or albumin fusion proteins comprising at least a fragment of variant of an antibody specific to a Therapeutic protein can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0245] One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a Therapeutic protein in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the Therapeutic protein is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the therapeutic protein. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0246] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody, antibody fragment, or albumin fusion protein comprising at least a fragment or variant of an antibody that binds a Therapeutic protein will then preferentially accumulate at the location of cells which contain the specific Therapeutic protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0247] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0248] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0249] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0250] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI). Antibodies that specifically detect the albumin fusion protein but not albumin or the therapeutic protein alone are a preferred embodiment. These can be used to detect the albumin fusion protein as described throughout the specification.

Kits

[0251] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate

such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[0252] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[0253] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[0254] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0255] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[0256] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0257] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Albumin Fusion Proteins

[0258] The present invention relates generally to albumin fusion proteins and methods of treating, preventing, or ameliorating diseases or disorders. As used herein, "albumin fusion protein" refers to a protein formed by the fusion of at least one molecule of albumin (or a fragment or variant thereof) to at least one molecule of a Therapeutic protein (or fragment or variant thereof). An albumin fusion protein of the invention comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion (i.e., the albumin fusion protein is generated by translation of a nucleic acid in which a polynucleotide encoding all or a portion of a Therapeutic protein is joined in-frame with a polynucleotide encoding all or a portion of albumin) or to one another. The Therapeutic protein and albumin protein, once part of the albumin fusion protein, may each be referred to as a "portion", "region" or "moiety" of the albumin fusion protein.

[0259] In a preferred embodiment, the invention provides an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 1 or Table 2. Polynucleotides encoding these albumin fusion proteins are also encompassed by the invention.

[0260] Preferred albumin fusion proteins of the invention, include, but are not limited to, albumin fusion proteins encoded by a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof); a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof) generated as described in Table 1, Table 2 or in the Examples; or a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof), further comprising, for example, one or more of the following elements: (1) a functional self-replicating vector (including but not limited to, a shuttle vector, an expression vector, an integration vector, and/or a replication system), (2) a region for initiation of transcription (e.g., a promoter region, such as for example, a regulatable or inducible promoter, a constitutive promoter), (3) a region

for termination of transcription, (4) a leader sequence, and (5) a selectable marker.

[0261] In one embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein (e.g., as described in Table 1) and a serum albumin protein. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment of a Therapeutic protein and a serum albumin protein. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active variant of a Therapeutic protein and a serum albumin protein. In preferred embodiments, the serum albumin protein component of the albumin fusion protein is the mature portion of serum albumin.

[0262] In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein, and a biologically active and/or therapeutically active fragment of serum albumin. In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a biologically active and/or therapeutically active variant of serum albumin. In preferred embodiments, the Therapeutic protein portion of the albumin fusion protein is the mature portion of the Therapeutic protein.

[0263] In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment or variant of a Therapeutic protein and a biologically active and/or therapeutically active fragment or variant of serum albumin. In preferred embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, the mature portion of a Therapeutic protein and the mature portion of serum albumin.

[0264] Preferably, the albumin fusion protein comprises HA as the N-terminal portion, and a Therapeutic protein as the C-terminal portion. Alternatively, an albumin fusion protein comprising HA as the C-terminal portion, and a Therapeutic protein as the N-terminal portion may also be used.

[0265] In other embodiments, the albumin fusion protein has a Therapeutic protein fused to both the N-terminus and the C-terminus of albumin. In a preferred embodiment, the Therapeutic proteins fused at the N- and C- termini are the same Therapeutic proteins. In an alternative preferred embodiment, the Therapeutic proteins fused at the N- and C- termini are different Therapeutic proteins. In another preferred embodiment, the Therapeutic proteins fused at the N- and C- termini are different Therapeutic proteins which may be used to treat or prevent the same or a related disease, disorder, or condition (e.g. as listed in the "Preferred Indication Y" column of Table 1). In another preferred embodiment, the Therapeutic proteins fused at the N- and C- termini are different Therapeutic proteins which may be used to treat, ameliorate, or prevent diseases or disorders (e.g. as listed in the "Preferred Indication Y" column of Table 1) which are known in the art to commonly occur in patients simultaneously, concurrently, or consecutively, or which commonly occur in patients in association with one another.

[0266] Albumin fusion proteins of the invention encompass proteins containing one, two, three, four, or more molecules of a given Therapeutic protein X or variant thereof fused to the N- or C- terminus of an albumin fusion protein of the invention, and/or to the N- and/or C- terminus of albumin or variant thereof. Molecules of a given Therapeutic protein X or variants thereof may be in any number of orientations, including, but not limited to, a 'head to head' orientation (e.g., wherein the N-terminus of one molecule of a Therapeutic protein X is fused to the N-terminus of another molecule of the Therapeutic protein X), or a 'head to tail' orientation (e.g., wherein the C-terminus of one molecule of a Therapeutic protein X is fused to the N-terminus of another molecule of Therapeutic protein X).

[0267] In one embodiment, one, two, three, or more tandemly oriented Therapeutic protein X polypeptides (or fragments or variants thereof) are fused to the N- or C- terminus of an albumin fusion protein of the invention, and/or to the N- and/or C- terminus of albumin or variant thereof.

[0268] Albumin fusion proteins of the invention further encompass proteins containing one, two, three, four, or more molecules of a given Therapeutic protein X or variant thereof fused to the N- or C- terminus of an albumin fusion protein of the invention, and/or to the N- and/or C- terminus of albumin or variant thereof, wherein the molecules are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Albumin fusion proteins comprising multiple Therapeutic protein X polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology. Linkers are particularly important when fusing a small peptide to the large HSA molecule. The peptide itself can be a linker by fusing tandem copies of the peptide or other known linkers can be used. Constructs that incorporate linkers are described in Table 2 or are apparent when examining SEQ ID NO:Y.

[0269] Further, albumin fusion proteins of the invention may also be produced by fusing a Therapeutic protein X or variants thereof to the N-terminal and/or C-terminal of albumin or variants thereof in such a way as to allow the formation of intramolecular and/or intermolecular multimeric forms. In one embodiment of the invention, albumin fusion proteins may be in monomeric or multimeric forms (i.e., dimers, trimers, tetramers and higher multimers). In a further embodiment of the invention, the Therapeutic protein portion of an albumin fusion protein may be in monomeric form or multimeric form (i.e., dimers, trimers, tetramers and higher multimers). In a specific embodiment, the Therapeutic protein portion of an albumin fusion protein is in multimeric form (i.e., dimers, trimers, tetramers and higher multimers), and the albumin protein portion is in monomeric form.

[0270] In addition to albumin fusion protein in which the albumin portion is fused N- terminal and/or C-terminal of the Therapeutic protein portion, albumin fusion proteins of the invention may also be produced by inserting the Therapeutic protein or peptide of interest (e.g., a Therapeutic

protein X as disclosed in Table 1, or an antibody that binds a Therapeutic protein or a fragment or variant thereof) into an internal region of HA. For instance, within the protein sequence of the HA molecule a number of loops or turns exist between the end and beginning of α-helices, which are stabilized by disulphide bonds. The loops, as determined from the crystal structure of HA (PDB identifiers 1AO6, 1BJ5, 1BKE, 1BM0, 1E7E to 1E7I and 1UOR) for the most part extend away from the body of the molecule. These loops are useful for the insertion, or internal fusion, of therapeutically active peptides, particularly those requiring a secondary structure to be functional, or Therapeutic proteins, to essentially generate an albumin molecule with specific biological activity.

[0271] Loops in human albumin structure into which peptides or polypeptides may be inserted to generate albumin fusion proteins of the invention include: Val54-Asn61, Thr76-Asp89, Ala92-Glu100, Gln170-Ala176, His 247 - Glu252, Glu 266 - Glu277, Glu 280-His288, Ala362-Glu368, Lys439-Pro447, Val462-Lys475, Thr478-Pro486, and Lys560-Thr566. In more preferred embodiments, peptides or polypeptides are inserted into the Val54-Asn61, Gln170-Ala176, and/or Lys560-Thr566 loops of mature human albumin (SEQ ID NO:1).

[0272] Peptides to be inserted may be derived from either phage display or synthetic peptide libraries screened for specific biological activity or from the active portions of a molecule with the desired function. Additionally, random peptide libraries may be generated within particular loops or by insertions of randomized peptides into particular loops of the HA molecule and in which all possible combinations of amino acids are represented.

[0273] Such library(s) could be generated on HA or domain fragments of HA by one of the following methods:

randomized mutation of amino acids within one or more peptide loops of HA or HA domain fragments. Either one, more or all the residues within a loop could be mutated in this manner;

replacement of, or insertion into one or more loops of HA or HA domain fragments (*i.e.*, internal fusion) of a randomized peptide(s) of length X_n (where X is an amino acid and n is the number of residues;

N-, C- or N- and C- terminal peptide/protein fusions in addition to (a) and/or (b).

[0274] The HA or HA domain fragment may also be made multifunctional by grafting the peptides derived from different screens of different loops against different targets into the same HA or HA domain fragment.

[0275] In preferred embodiments, peptides inserted into a loop of human serum albumin are peptide fragments or peptide variants of the Therapeutic proteins disclosed in Table 1. More particularly, the invention encompasses albumin fusion proteins which comprise peptide fragments or peptide variants at least 7 at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acids in length inserted into a loop of human serum albumin. The invention also encompasses albumin fusion proteins which comprise peptide fragments or peptide variants at least 7 at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acids fused to the N-terminus of human serum albumin. The invention also encompasses albumin fusion proteins which comprise peptide fragments or peptide variants at least 7 at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acids fused to the C-terminus of human serum albumin. For example, short peptides described in Table 1 and 2 (e.g., Therapeutic Y) can be inserted into the albumin loops.

[0276] Generally, the albumin fusion proteins of the invention may have one HA-derived region and one Therapeutic protein-derived region. Multiple regions of each protein, however, may be used to make an albumin fusion protein of the invention. Similarly, more than one Therapeutic protein may be used to make an albumin fusion protein of the invention. For instance, a Therapeutic protein may be fused to both the N- and C-terminal ends of the HA. In such a configuration, the Therapeutic protein portions may be the same or different Therapeutic protein molecules. The structure of bifunctional albumin fusion proteins may be represented as: X-HA-Y or Y-HA-X.

[0277] For example, an anti-BLyS™ scFv-HA-IFNα-2b fusion may be prepared to modulate the immune response to IFNα-2b by anti-BLyS™ scFv. An alternative is making a bi (or even multi) functional dose of HA-fusions *e.g.* HA-IFNα-2b fusion mixed with HA-anti-BLyS™ scFv fusion or other HA-fusions in various ratio's depending on function, half-life etc.

[0278] Bi- or multi-functional albumin fusion proteins may also be prepared to target the Therapeutic protein portion of a fusion to a target organ or cell type via protein or peptide at the opposite terminus of HA.

[0279] As an alternative to the fusion of known therapeutic molecules, the peptides could be obtained by screening libraries constructed as fusions to the N-, C- or N- and C- termini of HA, or domain fragment of HA, of typically 6, 8, 12, 20 or 25 or X_n (where X is an amino acid (aa) and n equals the number of residues) randomized amino acids, and in which all possible combinations of amino acids were represented. A particular advantage of this approach is that the peptides may be selected *in situ* on the HA molecule and the properties of the peptide would therefore be as selected for rather than, potentially, modified as might be the case for a peptide derived by any other method then being attached to HA.

[0280] Additionally, the albumin fusion proteins of the invention may include a linker peptide between the fused portions to provide greater physical separation between the moieties and thus maximize the accessibility of the Therapeutic protein portion, for instance, for binding to its cognate receptor. The linker peptide may consist of amino acids such that it is flexible or more rigid.

[0281] The linker sequence may be cleavable by a protease or chemically to yield the growth hormone related moiety. Preferably, the protease is one which is produced naturally by the host, for example the *S. cerevisiae* protease *kex2* or equivalent proteases.

[0282] Therefore, as described above, the albumin fusion proteins of the invention may have the following formula R1-L-R2; R2-L-R1; or R1-L-R2-L-R1, wherein R1 is at least one Therapeutic protein, peptide or polypeptide sequence, and not necessarily the same Therapeutic protein, L is a linker and R2 is a serum albumin sequence.

[0283] In preferred embodiments, albumin fusion proteins of the invention comprising a Therapeutic protein have a higher plasma stability compared to the plasma stability of the same Therapeutic protein when not fused to albumin. Plasma stability typically refers to the time period between when the Therapeutic protein is administered in vivo and carried into the bloodstream and when the therapeutic protein is degraded and cleared from the bloodstream, into an organ, such as the kidney or liver, that ultimately clears the Therapeutic protein from the body. Plasma stability is calculated in terms of the half-life of the Therapeutic protein in the bloodstream. The half-life of the Therapeutic protein in the bloodstream can be readily determined by common assays known in the art.

[0284] In preferred embodiments, Albumin fusion proteins of the invention comprising a Therapeutic protein have extended shelf life compared to the shelf life the same Therapeutic protein when not fused to albumin. Shelf-life typically refers to the time period over which the therapeutic activity of a Therapeutic protein in solution or in some other storage formulation, is stable without undue loss of therapeutic activity. Many of the Therapeutic proteins are highly labile in their unfused state. As described below, the typical shelf-life of these Therapeutic proteins is markedly prolonged upon incorporation into the albumin fusion protein of the invention.

[0285] Albumin fusion proteins of the invention with "prolonged" or "extended" shelf-life exhibit greater therapeutic activity relative to a standard that has been subjected to the same storage and handling conditions. The standard may be the unfused full-length Therapeutic protein. When the Therapeutic protein portion of the albumin fusion protein is an analog, a variant, or is otherwise altered or does not include the complete sequence for that protein, the prolongation of therapeutic activity may alternatively be compared to the unfused equivalent of that analog, variant, altered peptide or incomplete sequence. As an example, an albumin fusion protein of the invention may retain greater than about 100% of the therapeutic activity, or greater than about 105%, 110%, 120%, 130%, 150% or 200% of the therapeutic activity of a standard when subjected to the same storage and handling conditions as the standard when compared at a given time point.

[0286] Shelf-life may also be assessed in terms of therapeutic activity remaining after storage, normalized to therapeutic activity when storage began. Albumin fusion proteins of the invention with prolonged or extended shelf-life as exhibited by prolonged or extended therapeutic activity may retain greater than about 50% of the therapeutic activity, about 60%, 70%, 80%, or 90% or more of the therapeutic activity of the equivalent unfused Therapeutic protein when subjected to the same conditions.

Expression of Fusion Proteins

[0287] The albumin fusion proteins of the invention may be produced as recombinant molecules by secretion from yeast, a microorganism such as a bacterium, or a human or animal cell line. Preferably, the polypeptide is secreted from the host cells.

[0288] A particular embodiment of the invention comprises a DNA construct encoding a signal sequence effective for directing secretion in yeast, particularly a yeast-derived signal sequence (especially one which is homologous to the yeast host), and the fused molecule of the first aspect of the invention, there being no yeast-derived pro sequence between the signal and the mature polypeptide.

[0289] The *Saccharomyces cerevisiae* invertase signal is a preferred example of a yeast-derived signal sequence.

[0290] Conjugates of the kind prepared by Poznansky *et al.*, (FEBS Lett. 239:18 (1988)), in which separately-prepared polypeptides are joined by chemical cross-linking, are not contemplated.

[0291] The present invention also includes a cell, preferably a yeast cell transformed to express an albumin fusion protein of the invention. In addition to the transformed host cells themselves, the present invention also contemplates a culture of those cells, preferably a monoclonal (clonally homogeneous) culture, or a culture derived from a monoclonal culture, in a nutrient medium. If the polypeptide is secreted, the medium will contain the polypeptide, with the cells, or without the cells if they have been filtered or centrifuged away. Many expression systems are known and may be used, including bacteria (for example *E. coli* and *Bacillus subtilis*), yeasts (for example *Saccharomyces cerevisiae*, *Kluyveromyces lactis* and *Pichia pastoris*, filamentous fungi (for example *Aspergillus*), plant cells, animal cells and insect cells.

[0292] Preferred yeast strains to be used in the production of albumin fusion proteins are D88, DXY1 and BXP10. D88 [*leu2-3, leu2-122, can1, pra1, ubc4*] is a derivative of parent strain AH22*his*$^+$ (also known as DB1; see, e.g., Sleep *et al.* Biotechnology 8:42-46 (1990)). The strain contains a *leu2* mutation which allows for auxotropic selection of 2 micron-based plasmids that contain the LEU2 gene. D88 also exhibits a derepression of PRB1 in glucose excess. The PRB1 promoter is normally controlled by two checkpoints that monitor glucose levels and growth stage. The promoter is activated in wild type yeast upon glucose depletion and entry into stationary phase. Strain D88 exhibits the repression by glucose but maintains the induction upon entry into stationary phase. The PRA1 gene encodes a yeast vacuolar protease, YscA endoprotease A, that is localized in the ER. The UBC4 gene is in the ubiquitination pathway and is involved in targeting short lived and abnormal proteins for ubiquitin dependant degradation. Isolation of this ubc4 mutation was found to increase the copy number of an expression plasmid in the cell and cause an increased level of expression of a desired protein expressed from the plasmid (see, e.g., International Publication No. WO99/00504, hereby incorporated in its

entirety by reference herein).

[0293] DXY1, a derivative of D88, has the following genotype: [*leu2-3, leu2-122, can1, pra1, ubc4, ura3::yap3*]. In addition to the mutations isolated in D88, this strain also has a knockout of the YAP3 protease. This protease causes cleavage of mostly di-basic residues (RR, RK, KR, KK) but can also promote cleavage at single basic residues in proteins. Isolation of this yap3 mutation resulted in higher levels of full length HSA production (see, e.g., U.S. Patent No. 5,965,386 and Kerry-Williams et al., Yeast 14:161-169 (1998), hereby incorporated in their entireties by reference herein).

[0294] BXP10 has the following genotype: *leu2-3, leu2-122, can1, pra1, ubc4, ura3, yap3::URA3, lys2, hsp150::LYS2, pmt1::URA3*. In addition to the mutations isolated in DXY1, this strain also has a knockout of the PMT1 gene and the HSP150 gene. The PMT1 gene is a member of the evolutionarily conserved family of dolichyl-phosphate-D-mannose protein O-mannosyltransferases (Pmts). The transmembrane topology of Pmt1p suggests that it is an integral membrane protein of the endoplasmic reticulum with a role in O-linked glycosylation. This mutation serves to reduce/eliminate O-linked glycosylation of HSA fusions (see, e.g., International Publication No. WO00/44772, hereby incorporated in its entirety by reference herein). Studies revealed that the Hsp150 protein is inefficiently separated from rHA by ion exchange chromatography. The mutation in the HSP150 gene removes a potential contaminant that has proven difficult to remove by standard purification techniques. See, e.g., U.S. Patent No. 5,783,423, hereby incorporated in its entirety by reference herein.

[0295] The desired protein is produced in conventional ways, for example from a coding sequence inserted in the host chromosome or on a free plasmid. The yeasts are transformed with a coding sequence for the desired protein in any of the usual ways, for example electroporation. Methods for transformation of yeast by electroporation are disclosed in Becker & Guarente (1990) *Methods Enzymol.* 194, 182.

[0296] Successfully transformed cells, *i.e.*, cells that contain a DNA construct of the present invention, can be identified by well known techniques. For example, cells resulting from the introduction of an expression construct can be grown to produce the desired polypeptide. Cells can be harvested and lysed and their DNA content examined for the presence of the DNA using a method such as that described by Southern (1975) *J. Mol. Biol.* 98, 503 or Berent *et al.* (1985) *Biotech.* 3, 208. Alternatively, the presence of the protein in the supernatant can be detected using antibodies.

[0297] Useful yeast plasmid vectors include pRS403-406 and pRS413-416 and are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast Integrating plasmids (YIps) and incorporate the yeast selectable markers HIS3, 7RP1, LEU2 and URA3. Plasmids pRS413-416 are Yeast Centromere plasmids (Ycps).

[0298] Preferred vectors for making albumin fusion proteins for expression in yeast include pPPC0005, pScCHSA, pScNHSA, and pC4:HSA which are described in detail in Example 1. Figure 2 shows a map of the pPPC0005 plasmid that can be used as the base vector into which polynucleotides encoding Therapeutic proteins may be cloned to form HA-fusions. It contains a *PRB1 S. cerevisiae* promoter (PRB1p), a Fusion leader sequence (FL), DNA encoding HA (rHA) and an *ADH1 S. cerevisiae* terminator sequence. The sequence of the fusion leader sequence consists of the first 19 amino acids of the signal peptide of human serum albumin (SEQ ID NO:3) and the last five amino acids of the mating factor alpha 1 promoter (SLDKR, see EP-A-387 319 which is hereby incorporated by reference in its entirety).

[0299] The plasmids, pPPC0005, pScCHSA, pScNHSA, and pC4:HSA were deposited on April 11, 2001 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209 and given accession numbers ATCC PTA-3278, PTA-3276, PTA-3279, and PTA-3277, respectively. Another vector useful for expressing an albumin fusion protein in yeast the pSAC35 vector which is described in Sleep *et al.*, BioTechnology 8:42 (1990) which is hereby incorporated by reference in its entirety.

[0300] A yeast promoter that can be used to express the albumin fusion protein is the MET25 promoter. See, for example, Dominik Mumburg, Rolf Muller and Martin Funk. Nucleic Acids Research, 1994, Vol. 22, No. 25, pp. 5767-5768. The Met25 promoter is 383 bases long (bases −382 to −1) and the genes expressed by this promoter are also known as Met15, Met17, and YLR303W. A preferred embodiment uses the sequence below, where, at the 5' end of the sequence below, the Not 1 site used in the cloning is underlined and at the 3' end, the ATG start codon is underlined:

<u>GCGGCCGC</u>CGGATGCAAGGGTTCGAATCCCTTAGCTCTCATTATTTTTTGCTTTTTCTCTTGAGGTCACATGATCGCAAAATGGCAAA
TGGCACGTGAAGCTGTCGATATTGGGGAACTGTGGTGGTTGGCAAATGACTAATTAAGTTAGTCAAGGCGCCATCCTCATGAAAACT
GTGTAACATAATAACCGAAGTGTCGAAAAGGTGGCACCTTGTCCAATTGAACACGCTCGATGAAAAAAATAAGATATATATAAGGTT
AAGTAAAGCGTCTGTTAGAAAGGAAGTTTTTCCTTTTTCTTGCTCTCTTGTCTTTTCATCTACTATTTCCTTCGTGTAATACAGGGTCGT
CAGATACATAGATACAATTCTATTACCCCCATCCATACA<u>ATG</u> (SEQ ID NO:5)

[0301] Additional promoters that can be used to express the albumin fusion protein in yeast include the following:

a) the cbh1 promoter:

TCTAGAGTTGTGAAGTCGGTAATCCCGCTGTATAGTAATACGAGTCGCATCTAAATACTCCGAAGCTGCTGCGAACCCGGA
GAATCGAGATGTGCTGGAAAGCTTCTAGCGAGCGGCTAAATTAGCATGAAAGGCTATGAGAAATTCTGGAGACGGCTTGT
TGAATCATGGCGTTCCATTCTTCGACAAGCAAAGCGTTCCGTCGCAGTAGCAGGCACTCATTCCCGAAAAAACTCGGAGA
TTCCTAAGTAGCGATGGAACCGGAATAATATAATAGGCAATACATTGAGTTGCCTCGACGGTTGCAATGCAGGGGTACTG

AGCTTGGACATAACTGTTCCGTACCCCACCTCTTCTCAACCTTTGGCGTTTCCCTGATTCAGCGTACCCGTACAAGTCGTAA
TCACTATTAACCCAGACTGACCGGACGTGTTTTGCCCTTCATTTGGAGAAATAATGTCATTGCGATGTGTAATTTGCCTGCT
TGACCGACTGGGGCTGTTCGAAGCCCGAATGTAGGATTGTTATCCGAACTCTGCTCGTAGAGGCATGTTGTGAATCTGTGT
CGGGCAGGACACGCCTCGAAGGTTCACGGCAAGGGAAACCACCGATAGCAGTGTCTAGTAGCAACCTGTAAAGCCGCAA
TGCAGCATCACTGGAAAATACAAACCAATGGCTAAAAGTACATAAGTTAATGCCTAAAGAAGTCATATACCAGCGGCTAA
TAATTGTACAATCAAGTGGCTAAACGTACCGTAATTTGCCAACGGCTTGTGGGGTTGCAGAAGCAACGGCAAAGCCCCAC
TTCCCCACGTTTGTTTCTTCACTCAGTCCAATCTCAGCTGGTGATCCCCCAATTGGGTCGCTTGTTTGTTCCGGTGAAGTGA
AAGAAGACAGAGGTAAGAATGTCTGACTCGGAGCGTTTTGCATACAACCAAGGGCAGTGATGGAAGACAGTGAAATGTT
GACATTCAAGGAGTATTTAGCCAGGGATGCTTGAGTGTATCGTGTAAGGAGGTTTGTCTGCCGATACGACGAATACTGTAT
AGTCACTTCTGGTGAAGTGGTCCATATTGAAATGTAAGTCGGCACTGAACAGGCAAAAGATTGAGTTGAAACTGCCTAAG
ATCTCGGGCCCTCGGGCCTTCGGCCTTTGGGTGTACATGTTTGTGCTCCGGGCAAATGCAAAGTGTGGTAGGATCGAACAC
ACTGCTGCCTTTACCAAGCAGCTGAGGGTATGTGATAGGCAAATGTTCAGGGGCCACTGCATGGTTTCGAATAGAAAGAG
AAGCTTAGCCAAGAACAATAGCCGATAAAGATAGCCTCATTAAACGGAATGAGCTAGTAGGCAAAGTCAGCGAATGTGT
ATATATAAAGGTTCGAGGTCCGTGCCTCCCTCATGCTCTCCCCATCTACTCATCAACTCAGATCCTCCAGGAGACTTGTAC
ACCATCTTTTGAGGCACAGAAACCCAATAGTCAACCGCGGACTGGCATC (SEQ ID NO:113)

b) the cysD promoter from *Aspergillus nidulans*:

AGATCTGGTTCCTGAGTACATCTACCGATGCGCCTCGATCCCCCTCTTAGCCGCATGAGATTCCTACCATTTATGTCCTATCG
TTCAGGGTCCTATTTGGACCGCTAGAAATAGACTCTGCTCGATTTGTTTCCATTATTCACGCAATTACGATAGTATTTGGCTC
TTTTCGTTTGGCCCAGGTCAATTCGGGTAAGACGCGATCACGCCATTGTGGCCGCCGGCGTTGTGCTGCTGCTATTCCCCGC
ATATAAACAACCCCTCCACCAGTTCGTTGGGCTTTGCGAATGCTGTACTCTATTTCAAGTTGTCAAAAGAGAGGATTCAAAA
AATTATACCCCAGATATCAAAGATATCAAAGCCATC (SEQ ID NO:114)

c) a modified cbh1 promoter having the sequence:

TCTAGAGTTGTGAAGTCGGTAATCCCGCTGTATAGTAATACGAGTCGCATCTAAATACTCCGAAGCTGCTGCGAACCCGGA
GAATCGAGATGTGCTGGAAAGCTTCTAGCGAGCGGCTAAATTAGCATGAAAGGCTATGAGAAATTCTGGAGACGGCTTGT
TGAATCATGGCGTTCCATTCTTCGACAAGCAAAGCGTTCCGTCGCAGTAGCAGGCACTCATTCCCGAAAAAACTCGGAGA
TTCCTAAGTAGCGATGGAACCGGAATAATATAATAGGCAATACATTGAGTTGCCTCGACGGTTGCAATGCAGGGGTACTG
AGCTTGGACATAACTGTTCCGTACCCCACCTCTTCTCAACCTTTGGCGTTTCCCTGATTCAGCGTACCCGTACAAGTCGTAA
TCACTATTAACCCAGACTGACCGGACGTGTTTTGCCCTTCATTTGGAGAAATAATGTCATTGCGATGTGTAATTTGCCTGCT
TGACCGACTGGGGCTGTTCGAAGCCCGAATGTAGGATTGTTATCCGAACTCTGCTCGTAGAGGCATGTTGTGAATCTGTGT
CGGGCAGGACACGCCTCGAAGGTTCACGGCAAGGGAAACCACCGATAGCAGTGTCTAGTAGCAACCTGTAAAGCCGCAA
TGCAGCATCACTGGAAAATACAAACCAATGGCTAAAAGTACATAAGTTAATGCCTAAAGAAGTCATATACCAGCGGCTAA
TAATTGTACAATCAAGTGGCTAAACGTACCGTAATTTGCCAACGGCTTGTGGGGTTGCAGAAGCAACGGCAAAGCCCCAC
TTCCCCACGTTTGTTTCTTCACTCAGTCCAATCTCAGCTGGTGATCCCCCAATTGGGTCGCTTGTTTGTTCCGGTGAAGTGA
AAGAAGACAGAGGTAAGAATGTCTGACTCGGAGCGTTTTGCATACAACCAAGGGCAGTGATGGAAGACAGTGAAATGTT
GACATTCAAGGAGTATTTAGCCAGGGATGCTTGAGTGTATCGTGTAAGGAGGTTTGTCTGCCGATACGACGAATACTGTAT
AGTCACTTCTGGTGAAGTGGTCCATATTGAAATGTAAGTCGGCACTGAACAGGCAAAAGATTGAGTTGAAACTGCCTAAG
ATCTCGGGCCCTCGGGCCTTCGGCCTTTGGGTGTACATGTTTGTGCTCCGGGCAAATGCAAAGTGTGGTAGGATCGAACAC
ACTGCTGCCTTTACCAAGCAGCTGAGGGTATGTGATAGGCAAATGTTCAGGGGCCACTGCATGGTTTCGAATAGAAAGAG
AAGCTTAGCCTGCAGCCTCTTATCGAGAAAGAAATTACCGTCGCTCGTGATTTGTTTGCAAAAAGAACAAAACTGAAAAA
ACCCAGACACGCTCGACTTCCTGTCTTCCTATTGATTGCAGCTTCCAATTTCGTCACACAACAAGGTCCTAGCTTAGCCAA
GAACAATAGCCGATAAAGATAGCCTCATTAAACGGAATGAGCTAGTAGGCAAAGTCAGCGAATGTGTATATATAAAGGTT
CGAGGTCCGTGCCTCCCTCATGCTCTCCCCATCTACTCATCAACTCAGATCCTCCAGGAGACTTGTACACCATCTTTTGAGG
CACAGAAACCCAATAGTCAACCGCGGACTGGCATC (SEQ ID NO:115)

d) a cysD promoter from *Aspergillus nidulans* having the sequence:

AGATCTGGTTCCTGAGTACATCTACCGATGCGCCTCGATCCCCCTCTTAGCCGCATGAGATTCCTACCATTTATGTCCTATC
GTTCAGGGTCCTATTTGGACCGCTAGAAATAGACTCTGCTCGATTTGTTTCCATTATTCACGCAATTACGATAGTATTTGGC
TCTTTTCGTTTGGCCCAGGTCAATTCGGGTAAGACGCGATCACGCCATTGTGGCCGCCGGCGCTGCAGCCTCTTATCGAGA
AAGAAATTACCGTCGCTCGTGATTTGTTTGCAAAAAGAACAAAACTGAAAAAACCCAGACACGCTCGACTTCCTGTCTTCC
TATTGATTGCAGCTTCCAATTTCGTCACACAACAAGGTCCTACGCCGGCGTTGTGCTGCTGCTATTCCCCGCATATAAACA
ACCCCTCCACCAGTTCGTTGGGCTTTGCGAATGCTGTACTCTATTTCAAGTTGTCAAAAGAGAGGATTCAAAAAATTATAC
CCCAGATATCAAAGATATCAAAGCCATC (SEQ ID NO:116)

[0302] A variety of methods have been developed to operably link DNA to vectors via complementary cohesive termini. For instance, complementary homopolymer tracts can be added to the DNA segment to be inserted to the vector DNA. The vector and DNA segment are then joined by hydrogen bonding between the complementary homopolymeric tails to form recombinant DNA molecules.

[0303] Synthetic linkers containing one or more restriction sites provide an alternative method of joining the DNA segment to vectors. The DNA segment, generated by endonuclease restriction digestion, is treated with bacteriophage T4 DNA polymerase or E. coli DNA polymerase I, enzymes that remove protruding, gamma-single-stranded termini with their 3' 5'-exonucleolytic activities, and fill in recessed 3'-ends with their polymerizing activities.

[0304] The combination of these activities therefore generates blunt-ended DNA segments. The blunt-ended segments are then incubated with a large molar excess of linker molecules in the presence of an enzyme that is able to catalyze the ligation of blunt-ended DNA molecules, such as bacteriophage T4 DNA ligase. Thus, the products of the reaction are DNA segments carrying polymeric linker sequences at their ends. These DNA segments are then cleaved with the appropriate restriction enzyme and ligated to an expression vector that has been cleaved with an enzyme that produces termini compatible with those of the DNA segment.

[0305] Synthetic linkers containing a variety of restriction endonuclease sites are commercially available from a number of sources including International Biotechnologies Inc, New Haven, CT, USA.

[0306] A desirable way to modify the DNA in accordance with the invention, if, for example, HA variants are to be prepared, is to use the polymerase chain reaction as disclosed by Saiki *et al.* (1988) *Science* 239, 487-491. In this method the DNA to be enzymatically amplified is flanked by two specific oligonucleotide primers which themselves become incorporated into the amplified DNA. The specific primers may contain restriction endonuclease recognition sites which can be used for cloning into expression vectors using methods known in the art.

[0307] Exemplary genera of yeast contemplated to be useful in the practice of the present invention as hosts for expressing the albumin fusion proteins are *Pichia* (Hansenula), *Saccharomyces*, *Kluyveromyces*, *Candida*, *Torulopsis*, *Torulaspora*, *Schizosaccharomyces*, *Citeromyces*, *Pachysolen*, *Debaromyces*, *Metschunikowia*, *Rhodosporidium*, *Leucosporidium*, *Botryoascus*, *Sporidiobolus*, *Endomycopsis*, and the like. Preferred genera are those selected from the group consisting of *Saccharomyces*, *Schizosaccharomyces*, *Kluyveromyces*, *Pichia* and *Torulaspora*. Examples of *Saccharomyces spp.* are *S. cerevisiae*, *S. italicus and S. rouxii*.

[0308] Examples of Kluyveromyces spp. are K. fragilis, K. lactis and K. marxianus. A suitable Torulaspora species is T. delbrueckii. Examples of Pichia (Hansenula) spp. are P. angusta (formerly H. polymorpha), P. anomala (formerly H. anomala) and P. pastoris. Methods for the transformation of S. cerevisiae are taught generally in EP 251 744, EP 258 067 and WO 90/01063, all of which are incorporated herein by reference.

[0309] Preferred exemplary species of Saccharomyces include S. cerevisiae, S. italicus, S. diastaticus, and Zygosaccharomyces rouxii. Preferred exemplary species of Kluyveromyces include K. fragilis and K. lactis. Preferred exemplary species of Hansenula include H. polymorpha (now Pichia angusta), H. anomala (now Pichia anomala), and Pichia capsulata. Additional preferred exemplary species of Pichia include P. pastoris. Preferred exemplary species of Aspergillus include A. niger and A. nidulans. Preferred exemplary species of Yarrowia include Y. lipolytica. Many preferred yeast species are available from the ATCC. For example, the following preferred yeast species are available from the ATCC and are useful in the expression of albumin fusion proteins: Saccharomyces cerevisiae Hansen, teleomorph strain BY4743 yap3 mutant (ATCC Accession No. 4022731); Saccharomyces cerevisiae Hansen, teleomorph strain BY4743 hsp150 mutant (ATCC Accession No. 4021266); Saccharomyces cerevisiae Hansen, teleomorph strain BY4743 pmt1 mutant (ATCC Accession No. 4023792); Saccharomyces cerevisiae Hansen, teleomorph (ATCC Accession Nos. 20626; 44773; 44774; and 62995); Saccharomyces diastaticus Andrews et Gilliland ex van der Walt, teleomorph (ATCC Accession No. 62987); Kluyveromyces lactis (Dombrowski) van der Walt, teleomorph (ATCC Accession No. 76492); Pichia angusta (Teunisson et al.) Kurtzman, teleomorph deposited as Hansenula polymorpha de Morais et Maia, teleomorph (ATCC Accession No. 26012); Aspergillus niger van Tieghem, anamorph (ATCC Accession No. 9029); Aspergillus niger van Tieghem, anamorph (ATCC Accession No. 16404); Aspergillus nidulans (Eidam) Winter, anamorph (ATCC Accession No. 48756); and Yarrowia lipolytica (Wickerham et al.) van der Walt et von Arx, teleomorph (ATCC Accession No. 201847).

[0310] Suitable promoters for *S. cerevisiae* include those associated with the PGKI gene, GAL1 or GAL10 genes, CYCI, PHO5, TRPI, ADHI, ADH2, the genes for glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, triose phosphate isomerase, phosphoglucose isomerase, glucokinase, alpha-mating factor pheromone, [a mating factor pheromone], the PRBI promoter, the GUT2 promoter, the GPDI promoter, and hybrid promoters involving hybrids of parts of 5' regulatory regions with parts of 5' regulatory regions of other promoters or with upstream activation sites (*e.g.* the promoter of EP-A-258 067).

[0311] Convenient regulatable promoters for use in *Schizosaccharomyces pombe* are the thiamine-repressible promoter from the nmt gene as described by Maundrell (1990) *J. Biol. Chem.* 265, 10857-10864 and the glucose repressible jbpl gene promoter as described by Hoffman & Winston (1990) *Genetics* 124, 807-816.

[0312] Methods of transforming *Pichia* for expression of foreign genes are taught in, for example, Cregg *et al.* (1993), and various Phillips patents (*e.g.* US 4 857 467, incorporated herein by reference), and *Pichia* expression kits are commercially available from Invitrogen BV, Leek, Netherlands, and Invitrogen Corp., San Diego, California. Suitable promoters include AOXI and AOX2. Gleeson *et al.* (1986) J. Gen. Microbiol.

132, 3459-3465 include information on *Hansenula* vectors and transformation, suitable promoters being MOX1 and FMD1; whilst EP 361 991, Fleer *et al.* (1991) and other- publications from Rhone-Poulenc Rorer teach how to express foreign proteins in *Kluyveromyces* spp., a suitable promoter being PGKL

[0313] The transcription termination signal is preferably the 3' flanking sequence of a eukaryotic gene which contains proper signals for transcription termination and polyadenylation. Suitable 3' flanking sequences may, for example, be those of the gene naturally linked to the expression control sequence used, *i.e.* may correspond to the promoter. Alternatively, they may be different in which case the termination signal of the *S. cerevisiae* ADHI gene is preferred.

[0314] The desired albumin fusion protein may be initially expressed with a secretion leader sequence, which may be any leader effective in the yeast chosen. Leaders useful in yeast include any of the following:

a) the MPIF-1 signal sequence (e.g., amino acids 1-21 of GenBank Accession number AAB51134) MKVSVAALSCLMLVTALGSQA (SEQ ID NO:6)
b) the stanniocalcin signal sequence (MLQNSAVLLLLVISASA, SEQ ID NO:7)
c) the pre-pro region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYSRGVFRR, SEQ ID NO:8)
d) the pre region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYS, SEQ ID NO:9) or variants thereof, such as, for example, MKWVSFISLLFLFSSAYS, (SEQ ID NO:10)
e) the invertase signal sequence (e.g., MLLQAFLFLLAGFAAKISA, SEQ ID NO:11)
f) the yeast mating factor alpha signal sequence (e.g., MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVAVLPFSNSTNNGLLFINTTIASIAAKEEGVSLEKR, SEQ ID NO:12 or MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVAVLPFSNSTNNGLLFINTTIASIAAKEEGVSLDKR, SEQ ID NO:12)
g) *K. lactis* killer toxin leader sequence
h) a hybrid signal sequence (e.g., MKWVSFISLLFLFSSAYSRSLEKR, SEQ ID NO:13)
i) an HSA/MFα-1 hybrid signal sequence (also known as HSA/kex2) (e.g., MKWVSFISLLFLFSSAYSRSLDKR, SEQ ID NO:14)
j) a *K. lactis* killer/ MFα-1 fusion leader sequence (e.g., MNIFYIFLFLLSFVQGSLDKR, SEQ ID NO:15)
k) the Immunoglobulin Ig signal sequence (e.g., MGWSCIILFLVATATGVHS, SEQ ID NO:16)
l) the Fibulin B precursor signal sequence (e.g., MERAAPSRRVPLPLLLLGGLALLAAGVDA, SEQ ID NO:17)
m) the clusterin precursor signal sequence (e.g., MMKTLLLFVGLLLTWESGQVLG, SEQ ID NO:18)
n) the insulin-like growth factor-binding protein 4 signal sequence (e.g., MLPLCLVAALLLAAGPGPSLG, SEQ ID NO:19)
o) variants of the pre-pro-region of the HSA signal sequence such as, for example,
   MKWVSFISLLFLFSSAYSRGVFRR (SEQ ID NO:20),
   MKWVTFISLLFLFAGVLG (SEQ ID NO:21),
   MKWVTFISLLFLFSGVLG (SEQ ID NO:22),
   MKWVTFISLLFLFGGVLG (SEQ ID NO:23),
   Modified HSA leader HSA #64 - MKWVTFISLLFLFAGVSG (SEQ ID NO:24);
   Modified HSA leader HSA #66 - MKWVTFISLLFLFGGVSG (SEQ ID NO:25);
   Modified HSA (A14) leader – MKWVTFISLLFLFAGVSG (SEQ ID NO:26);
   Modified HSA (S14) leader (also known as modified HSA #65) – MKWVTFISLLFLFSGVSG (SEQ ID NO:27),
   Modified HSA (G14) leader – MKWVTFISLLFLFGGVSG (SEQ ID NO:28), or MKWVTFISLLFLFGGVLGDLHKS (SEQ ID NO:29)
p) a consensus signal sequence (MPTWAWWLFLVLLLALWAPARG, SEQ ID NO:30)
q) acid phosphatase (PH05) leader (e.g., MFKSVVYSILAASLANA SEQ ID NO:31)
r) the pre-sequence of MFoz-1
s) the pre-sequence of 0 glucanase (BGL2)
t) killer toxin leader
u) the presequence of killer toxin
v) k. lactis killer toxin prepro (29 amino acids; 16 amino acids of pre and 13 amino acids of pro) MNIFYIFLFLLSFVQGLEHTHRRGSLDKR (SEQ ID NO:32)
w) *S. diastaticus* glucoamylase II secretion leader sequence
x) *S. carlsbergensis* α-galactosidase (MEL1) secretion leader sequence
y) *Candida glucoarnylase* leader sequence
z) The hybrid leaders disclosed in EP-A-387 319 (herin incorporated by reference)

aa) the gp67 signal sequence (in conjunction with baculoviral expression systems) (e.g., amino acids 1-19 of GenBank Accession Number AAA72759) or

bb) the natural leader of the therapeutic protein X;

cc) S. cerevisiae invertase (SUC2) leader, as disclosed in JP 62-096086 (granted as 911036516, herein incorporate by reference); or

dd) Inulinase – MKLAYSLLLPLAGVSASVINYKR (SEQ ID NO:33).

ee) A modified TA57 propeptide leader variant #1 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNSGGLDVVGLISMAKR (SEQ ID NO:34)

ff) A modified TA57 propeptide leader variant #2 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNSGGLDVVGLISMAEEGEPKR (SEQ ID NO:35)

gg) A consensus signal peptide – MWWRLWWLLLLLLLLWPMVWA (SEQ ID NO:111)

hh) A modified HSA/kex2 signal sequence- MKWVSFISLLFLFSSAYSGSLDKR (SEQ ID NO:112)

ii) A consensus signal peptide #2 – MRPTWAWWLFLVLLLALWAPARG (SEQ ID NO:105)

Additional Methods of Recombinant and Synthetic Production of Albumin Fusion Proteins

[0315] The present invention also relates to vectors containing a polynucleotide encoding an albumin fusion protein of the present invention, host cells, and the production of albumin fusion proteins by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[0316] The polynucleotides encoding albumin fusion proteins of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

[0317] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli lac, trp, phoA* and *tac* promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[0318] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418, glutamine synthase, or neomycin resistance for eukaryotic cell culture, and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, Streptomyces and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, NSO, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[0319] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

[0320] In one embodiment, polynucleotides encoding an albumin fusion protein of the invention may be fused to signal sequences which will direct the localization of a protein of the invention to particular compartments of a prokaryotic or eukaryotic cell and/or direct the secretion of a protein of the invention from a prokaryotic or eukaryotic cell. For example, in *E. coli*, one may wish to direct the expression of the protein to the periplasmic space. Examples of signal sequences or proteins (or fragments thereof) to which the albumin fusion proteins of the invention may be fused in order to direct the expression of the polypeptide to the periplasmic space of bacteria include, but are not limited to, the *pelB* signal sequence, the maltose binding protein (MBP) signal sequence, MBP, the *ompA* signal sequence, the signal sequence of the periplasmic *E. coli* heat-labile enterotoxin B-subunit, and the signal sequence of alkaline phosphatase. Several vectors are commercially available for the construction of fusion proteins which will direct the localization of a protein, such as the pMAL series of vectors (particularly the pMAL-p series) available from New England Biolabs. In a specific embodiment, polynucleotides albumin fusion proteins of the invention may be fused to the *pelB* pectate lyase signal sequence to increase the efficiency of expression and purification of such polypeptides in Gram-negative bacteria. *See*, U.S. Patent Nos. 5,576,195 and 5,846,818, the contents of which are herein incorporated by reference in their entireties.

[0321] Examples of signal peptides that may be fused to an albumin fusion protein of the invention in order to direct its secretion in mammalian cells include, but are not limited to:

a) the MPIF-1 signal sequence (e.g., amino acids 1-21 of GenBank Accession number AAB51134) MKVSVAALSCLMLVTALGSQA (SEQ ID NO:6)

b) the stanniocalcin signal sequence (MLQNSAVLLLLVISASA, SEQ ID NO:7)

c) the pre-pro region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYSRGVFRR, SEQ ID NO:8)

d) the pre region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYS, SEQ ID NO:9) or variants thereof, such as, for example, MKWVSFISLLFLFSSAYS, (SEQ ID NO:10)

e) the invertase signal sequence (e.g., MLLQAFLFLLAGFAAKISA, SEQ ID NO:11)

f) the yeast mating factor alpha signal sequence (e.g., MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVAVLPFSNSTNNGLLFINTTIASIAAKEEGVSLEKR, SEQ ID NO:12 or MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVAVLPFSNSTNNGLLFINTTIASIAAKEEGVSLDKR, SEQ ID NO:12)

g) *K. lactis* killer toxin leader sequence

h) a hybrid signal sequence (e.g., MKWVSFISLLFLFSSAYSRSLEKR, SEQ ID NO:13)

i) an HSA/MFα-1 hybrid signal sequence (also known as HSA/kex2) (e.g., MKWVSFISLLFLFSSAYSRSLDKR, SEQ ID NO:14)

j) a *K. lactis* killer/ MFα-1 fusion leader sequence (e.g., MNIFYIFLFLLSFVQGSLDKR, SEQ ID NO:15)

k) the Immunoglobulin Ig signal sequence (e.g., MGWSCIILFLVATATGVHS, SEQ ID NO:16)

l) the Fibulin B precursor signal sequence (e.g., MERAAPSRRVPLPLLLLGGLALLAAGVDA, SEQ ID NO:17)

m) the clusterin precursor signal sequence (e.g., MMKTLLLFVGLLLTWESGQVLG, SEQ ID NO:18)

n) the insulin-like growth factor-binding protein 4 signal sequence (e.g., MLPLCLVAALLLAAGPGPSLG, SEQ ID NO:19)

o) variants of the pre-pro-region of the HSA signal sequence such as, for example,
MKWVSFISLLFLFSSAYSRGVFRR (SEQ ID NO:20),
MKWVTFISLLFLFAGVLG (SEQ ID NO:21),
MKWVTFISLLFLFSGVLG (SEQ ID NO:22),
MKWVTFISLLFLFGGVLG (SEQ ID NO:23),
Modified HSA leader HSA #64 - MKWVTFISLLFLFAGVSG (SEQ ID NO:24);
Modified HSA leader HSA #66 - MKWVTFISLLFLFGGVSG (SEQ ID NO:25);
Modified HSA (A14) leader – MKWVTFISLLFLFAGVSG (SEQ ID NO:26);
Modified HSA (S14) leader (also known as modified HSA #65) – MKWVTFISLLFLFSGVSG (SEQ ID NO:27),
Modified HSA (G14) leader – MKWVTFISLLFLFGGVSG (SEQ ID NO:28), or MKWVTFISLLFLFGGVLGDLHKS (SEQ ID NO:29)

p) a consensus signal sequence (MPTWAWWLFLVLLLALWAPARG, SEQ ID NO:30)

q) acid phosphatase (PH05) leader (e.g., MFKSVVYSILAASLANA SEQ ID NO:31)

r) the pre-sequence of MFoz-1

s) the pre-sequence of 0 glucanase (BGL2)

t) killer toxin leader

u) the presequence of killer toxin

v) k. lactis killer toxin prepro (29 amino acids; 16 amino acids of pre and 13 amino acids of pro) MNIFYIFLFLLSFVQGLEHTHRRGSLDKR (SEQ ID NO:32)

w) *S. diastaticus* glucoamylase II secretion leader sequence

x) *S. carlsbergensis* α-galactosidase (MEL1) secretion leader sequence

y) *Candida glucoamylase* leader sequence

z) The hybrid leaders disclosed in EP-A-387 319 (herin incorporated by reference)

aa) the gp67 signal sequence (in conjunction with baculoviral expression systems) (e.g., amino acids 1-19 of GenBank Accession Number AAA72759) or

bb) the natural leader of the therapeutic protein X;

cc) S. cerevisiae invertase (SUC2) leader, as disclosed in JP 62-096086 (granted as 911036516, herein incorporate by reference); or

dd) Inulinase – MKLAYSLLLPLAGVSASVINYKR (SEQ ID NO:33).

ee) A modified TA57 propeptide leader variant #1 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNSGGLDVVGLISMAKR (SEQ ID NO:34)

ff) A modified TA57 propeptide leader variant #2 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNSGGLDVVGLISMAEEGEPKR (SEQ ID NO:35)

gg) A consensus signal peptide – MWWRLWWLLLLLLLLWPMVWA (SEQ ID NO:111)

jj) A modified HSA/kex2 signal sequence- MKWVSFISLLFLFSSAYSGSLDKR (SEQ ID NO:112)

kk) A consensus signal peptide #2 – MRPTWAWWLFLVLLLALWAPARG (SEQ ID NO:105)

[0322] In a preferred embodiment, the modified HSA/kex2 signal sequence (SEQ ID NO:112) is fused to the amino terminus of an albumin fusion protein, including fusion proteins comprising albumin and a therapeutic protein as described herein, as well as albumin fusion proteins disclosed in WO93/15199; WO97/24445; WO03/60071; WO03/59934; and PCT/US04/01369, each of which are incorporated herein by reference in their entireties. The modified HSA/kex2 signal sequence is based on the HSA/kex2 signal sequence (SEQ ID NO:14) disclosed, e.g., in Sleep et al., Biotechnology 1990, vol. 8, pp. 42-46; and US Patent 5,302,697, both of which are incorporated herein by reference in their entireties. The modified HSA/kex2 leader sequence disclosed herein contains a non-conservative amino acid substitution (Arg to Gly) at residue 19 of the parent signal peptide. The modified HSA/kex2 signal peptide has been found to produce unexpectedly better expression yield and/or better cleavage efficiency of albumin fusion proteins when expressed in yeast than the unmodified HSA/kex2 signal sequence. Variants of the modified HSA/kex2 signal peptide are also encompassed by the invention. In particular the Gly residue at position 19 of SEQ ID NO:112 may be substituted with a Pro residue. Other conservative substitution variants of the modified HSA/kex2 signal sequence are also contemplated. Nucleic acids encoding the modified HSA/kex2 signal sequence of SEQ ID NO:112, as well as conservative substitution variants thereof, are also encompassed by the invention.

[0323] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NSO) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657, which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al., Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

[0324] The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

[0325] Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., the coding sequence corresponding to a Therapeutic protein may be replaced with an albumin fusion protein corresponding to the Therapeutic protein), and/or to include genetic material (e.g., heterologous polynucleotide sequences such as for example, an albumin fusion protein of the invention corresponding to the Therapeutic protein may be included). The genetic material operably associated with the endogenous polynucleotide may activate, alter, and/or amplify endogenous polynucleotides.

[0326] In addition, techniques known in the art may be used to operably associate heterologous polynucleotides (e.g., polynucleotides encoding an albumin protein, or a fragment or variant thereof) and/or heterologous control regions (e.g., promoter and/or enhancer) with endogenous polynucleotide sequences encoding a Therapeutic protein via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al., Proc. Natl. Acad. Sci. USA 86*:8932-8935 (1989); and Zijlstra *et al., Nature 342*:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0327] Albumin fusion proteins of the invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography,

hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, hydrophobic charge interaction chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

[0331] In preferred embodiments the albumin fusion proteins of the invention are purified using Anion Exchange Chromatography including, but not limited to, chromatography on Q-sepharose, DEAE sepharose, poros HQ, poros DEAE, Toyopearl Q, Toyopearl QAE, Toyopearl DEAE, Resource/Source Q and DEAE, Fractogel Q and DEAE columns.

[0332] In specific embodiments the albumin fusion proteins of the invention are purified using Cation Exchange Chromatography including, but not limited to, SP-sepharose, CM sepharose, poros HS, poros CM, Toyopearl SP, Toyopearl CM, Resource/Source S and CM, Fractogel S and CM columns and their equivalents and comparables.

[0333] In specific embodiments the albumin fusion proteins of the invention are purified using Hydrophobic Interaction Chromatography including, but not limited to, Phenyl, Butyl, Methyl, Octyl, Hexyl-sepharose, poros Phenyl, Butyl, Methyl, Octyl, Hexyl, Toyopearl Phenyl, Butyl, Methyl, Octyl, Hexyl Resource/Source Phenyl, Butyl, Methyl, Octyl, Hexyl, Fractogel Phenyl, Butyl, Methyl, Octyl, Hexyl columns and their equivalents and comparables.

[0334] In specific embodiments the albumin fusion proteins of the invention are purified using Size Exclusion Chromatography including, but not limited to, sepharose S100, S200, S300, superdex resin columns and their equivalents and comparables.

[0335] In specific embodiments the albumin fusion proteins of the invention are purified using Affinity Chromatography including, but not limited to, Mimetic Dye affinity, peptide affinity and antibody affinity columns that are selective for either the HSA or the "fusion target" molecules.

[0336] In preferred embodiments albumin fusion proteins of the invention are purified using one or more Chromatography methods listed above. In other preferred embodiments, albumin fusion proteins of the invention are purified using one or more of the following Chromatography columns, Q sepharose FF column, SP Sepharose FF column, Q Sepharose High Performance Column, Blue Sepharose FF column , Blue Column, Phenyl Sepharose FF column, DEAE Sepharose FF, or Methyl Column.

[0337] Additionally, albumin fusion proteins of the invention may be purified using the process described in PCT International Publication WO 00/44772 which is herein incorporated by reference in its entirety. One of skill in the art could easily modify the process described therein for use in the purification of albumin fusion proteins of the invention.

[0338] Albumin fusion proteins of the present invention may be recovered from: products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, albumin fusion proteins of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0339] In one embodiment, the yeast *Pichia pastoris* is used to express albumin fusion proteins of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O_2. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O_2. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See Ellis, S.B., *et al., Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J, *et al., Yeast* 5:167-77 (1989); Tschopp, J.F., *et al., Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

[0340] In one example, the plasmid vector pPIC9K is used to express DNA encoding an albumin fusion protein of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[0341] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[0342] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide encoding an

albumin fusion protein of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[0343] In addition, albumin fusion proteins of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0344] The invention encompasses albumin fusion proteins of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

[0345] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The albumin fusion proteins may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[0346] Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine (^{121}I, ^{123}I, ^{125}I, ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{111}In, ^{112}In, ^{113m}In, ^{115m}In), technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, and ^{97}Ru.

[0347] In specific embodiments, albumin fusion proteins of the present invention or fragments or variants thereof are attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, ^{177}Lu, ^{90}Y, ^{166}Ho, and ^{153}Sm, to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is ^{111}In. In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is ^{90}Y. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

[0348] As mentioned, the albumin fusion proteins of the invention may be modified by either natural processes, such as post-translational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Polypeptides of the invention may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POST-TRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

[0349] Albumin fusion proteins of the invention and antibodies that bind a Therapeutic protein or fragments or variants thereof can be fused to

marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[0350] Further, an albumin fusion protein of the invention may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0351] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol., 6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors. Techniques for conjugating such therapeutic moiety to proteins (e.g., albumin fusion proteins) are well known in the art.

[0352] Albumin fusion proteins may also be attached to solid supports, which are particularly useful for immunoassays or purification of polypeptides that are bound by, that bind to, or associate with albumin fusion proteins of the invention. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0353] Albumin fusion proteins, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

[0354] In embodiments where the albumin fusion protein of the invention comprises only the VH domain of an antibody that binds a Therapeutic protein, it may be necessary and/or desirable to coexpress the fusion protein with the VL domain of the same antibody that binds a Therapeutic protein, such that the VH-albumin fusion protein and VL protein will associate (either covalently or non-covalently) post-translationally.

[0355] In embodiments where the albumin fusion protein of the invention comprises only the VL domain of an antibody that binds a Therapeutic protein, it may be necessary and/or desirable to coexpress the fusion protein with the VH domain of the same antibody that binds a Therapeutic protein, such that the VL-albumin fusion protein and VH protein will associate (either covalently or non-covalently) post-translationally.

[0356] Some Therapeutic antibodies are bispecific antibodies, meaning the antibody that binds a Therapeutic protein is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. In order to create an albumin fusion protein corresponding to that Therapeutic protein, it is possible to create an albumin fusion protein which has an scFv fragment fused to both the N- and C- terminus of the albumin protein moiety. More particularly, the scFv fused to the N-terminus of albumin would correspond to one of the heavy/light (VH/VL) pairs of the original antibody that binds a Therapeutic protein and the scFv fused to the C-terminus of albumin would correspond to the other heavy/light (VH/VL) pair of the original antibody that binds a Therapeutic protein.

[0357] Also provided by the invention are chemically modified derivatives of the albumin fusion proteins of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The albumin fusion proteins may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0358] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the

desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a Therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0359] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al., Appl. Biochem. Biotechnol. 56*:59-72 (1996); Vorobjev *et al., Nucleosides Nucleotides 18*:2745-2750 (1999); and Caliceti *et al., Bioconjug. Chem. 10*:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0360] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., Exp. Hematol. 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0361] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[0362] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0363] As indicated above, pegylation of the albumin fusion proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the albumin fusion protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[0364] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

[0365] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0366] The number of polyethylene glycol moieties attached to each albumin fusion protein of the invention (i.e., the degree of substitution) may

also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

[0367] The polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

[0368] The presence and quantity of albumin fusion proteins of the invention may be determined using ELISA, a well known immunoassay known in the art. In one ELISA protocol that would be useful for detecting/quantifying albumin fusion proteins of the invention, comprises the steps of coating an ELISA plate with an anti-human serum albumin antibody, blocking the plate to prevent non-specific binding, washing the ELISA plate, adding a solution containing the albumin fusion protein of the invention (at one or more different concentrations), adding a secondary anti-Therapeutic protein specific antibody coupled to a detectable label (as described herein or otherwise known in the art), and detecting the presence of the secondary antibody. In an alternate version of this protocol, the ELISA plate might be coated with the anti-Therapeutic protein specific antibody and the labeled secondary reagent might be the anti-human albumin specific antibody.

Uses of the Polynucleotides

[0369] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[0370] The polynucleotides of the present invention are useful to produce the albumin fusion proteins of the invention. As described in more detail below, polynucleotides of the invention (encoding albumin fusion proteins) may be used in recombinant DNA methods useful in genetic engineering to make cells, cell lines, or tissues that express the albumin fusion protein encoded by the polynucleotides encoding albumin fusion proteins of the invention.

[0371] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy", and Examples 61 and 62).

Uses of the Polypeptides

[0372] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[0373] Albumin fusion proteins of the invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[0374] Albumin fusion proteins can be used to assay levels of polypeptides in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0375] Albumin fusion proteins of the invention can also be detected *in vivo* by imaging. Labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, nuclear magnetic resonance (NMR) or electron spin relaxtion (ESR). For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the albumin fusion protein by labeling of nutrients given to a cell line expressing the albumin fusion protein of the invention.

[0376] An albumin fusion protein which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc, (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F, ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for

example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled albumin fusion protein will then preferentially accumulate at locations in the body (e.g., organs, cells, extracellular spaces or matrices) where one or more receptors, ligands or substrates (corresponding to that of the Therapeutic protein used to make the albumin fusion protein of the invention) are located. Alternatively, in the case where the albumin fusion protein comprises at least a fragment or variant of a Therapeutic antibody, the labeled albumin fusion protein will then preferentially accumulate at the locations in the body (e.g., organs, cells, extracellular spaces or matrices) where the polypeptides/epitopes corresponding to those bound by the Therapeutic antibody (used to make the albumin fusion protein of the invention) are located. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)). The protocols described therein could easily be modified by one of skill in the art for use with the albumin fusion proteins of the invention.

[0377] In one embodiment, the invention provides a method for the specific delivery of albumin fusion proteins of the invention to cells by administering albumin fusion proteins of the invention (e.g., polypeptides encoded by polynucleotides encoding albumin fusion proteins of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a Therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0378] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering albumin fusion proteins of the invention in association with toxins or cytotoxic prodrugs.

[0379] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi, or other radioisotopes such as, for example, ^{103}Pd, ^{133}Xe, ^{131}I, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{35}S, ^{90}Y, ^{153}Sm, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{90}Yttrium, ^{117}Tin, ^{186}Rhenium, ^{166}Holmium, and ^{188}Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{90}Y. In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{111}In. In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{131}I.

[0380] Techniques known in the art may be applied to lable polypeptides of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274;119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[0381] The albumin fusion proteins of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those described herein under the section heading "Biological Activities," below.

[0382] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a certain polypeptide in cells or body fluid of an individual using an albumin fusion protein of the invention; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0383] Moreover, albumin fusion proteins of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement

absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[0384] In particular, albumin fusion proteins comprising of at least a fragment or variant of a Therapeutic antibody can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an albumin fusion protein comprising of at least a fragment or variant of a Therapeutic antibody can bind, and/or neutralize the polypeptide to which the Therapeutic antibody used to make the albumin fusion protein specifically binds, and/or reduce overproduction of the polypeptide to which the Therapeutic antibody used to make the albumin fusion protein specifically binds. Similarly, administration of an albumin fusion protein comprising of at least a fragment or variant of a Therapeutic antibody can activate the polypeptide to which the Therapeutic antibody used to make the albumin fusion protein specifically binds, by binding to the polypeptide bound to a membrane (receptor).

[0385] At the very least, the albumin fusion proteins of the invention of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Albumin fusion proteins of the invention can also be used to raise antibodies, which in turn may be used to measure protein expression of the Therapeutic protein, albumin protein, and/or the albumin fusion protein of the invention from a recombinant cell, as a way of assessing transformation of the host cell, or in a biological sample. Moreover, the albumin fusion proteins of the present invention can be used to test the biological activities described herein.

Diagnostic Assays

[0386] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those described for each Therapeutic protein in the corresponding row of Table 1 and herein under the section headings "Immune Activity," "Blood Related Disorders," "Hyperproliferative Disorders," "Renal Disorders," "Cardiovascular Disorders," "Respiratory Disorders," "Anti-Angiogenesis Activity," "Diseases at the Cellular Level," "Wound Healing and Epithelial Cell Proliferation," "Neural Activity and Neurological Diseases," "Endocrine Disorders," "Reproductive System Disorders," "Infectious Disease," "Regeneration," and/or "Gastrointestinal Disorders," *infra*.

[0387] For a number of disorders, substantially altered (increased or decreased) levels of gene expression can be detected in tissues, cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, that is, the expression level in tissues or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a disorder, which involves measuring the expression level of the gene encoding a polypeptide in tissues, cells or body fluid from an individual and comparing the measured gene expression level with a standard gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue.

[0388] The present invention is also useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed gene expression will experience a worse clinical outcome.

[0389] By "assaying the expression level of the gene encoding a polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of a particular polypeptide (e.g. a polypeptide corresponding to a Therapeutic protein disclosed in Table 1) or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0390] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing polypeptides of the invention (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) and tissue sources found to express the full length or fragments thereof of a polypeptide or mRNA. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0391] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the polypeptides of the invention are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

[0392] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of polypeptides that

bind to, are bound by, or associate with albumin fusion proteins of the invention, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting abnormal expression of polypeptides that bind to, are bound by, or associate with albumin fusion proteins compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide that bind to, are bound by, or associate with albumin fusion proteins of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying polypeptide levels in a biological sample can occur using any art-known method.

[0393] Assaying polypeptide levels in a biological sample can occur using a variety of techniques. For example, polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987)). Other methods useful for detecting polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0394] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the gene of interest (such as, for example, cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the gene.

[0395] For example, albumin fusion proteins may be used to quantitatively or qualitatively detect the presence of polypeptides that bind to, are bound by, or associate with albumin fusion proteins of the present invention. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled albumin fusion protein coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0396] In a preferred embodiment, albumin fusion proteins comprising at least a fragment or variant of an antibody that specifically binds at least a Therapeutic protein disclosed herein (e.g., the Therapeutic proteins disclosed in Table 1) or otherwise known in the art may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0397] The albumin fusion proteins of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of polypeptides that bind to, are bound by, or associate with an albumin fusion protein of the present invention. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or polypeptide of the present invention. The albumin fusion proteins are preferably applied by overlaying the labeled albumin fusion proteins onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the polypeptides that bind to, are bound by, or associate with albumin fusion proteins, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[0398] Immunoassays and non-immunoassays that detect polypeptides that bind to, are bound by, or associate with albumin fusion proteins will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

[0399] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled albumin fusion protein of the invention. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

[0400] By "solid phase support or carrier" is intended any support capable of binding a polypeptide (e.g., an albumin fusion protein, or polypeptide that binds, is bound by, or associates with an albumin fusion protein of the invention.) Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to a polypeptide. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other

suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0401] The binding activity of a given lot of albumin fusion protein may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[0402] In addition to assaying polypeptide levels in a biological sample obtained from an individual, polypeptide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, albumin fusion proteins of the invention are used to image diseased or neoplastic cells.

[0403] Labels or markers for *in vivo* imaging of albumin fusion proteins of the invention include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the albumin fusion protein by labeling of nutrients of a cell line (or bacterial or yeast strain) engineered.

[0404] Additionally, albumin fusion proteins of the invention whose presence can be detected, can be administered. For example, albumin fusion proteins of the invention labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further, such polypeptides can be utilized for *in vitro* diagnostic procedures.

[0405] A polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled albumin fusion protein will then preferentially accumulate at the locations in the body which contain a polypeptide or other substance that binds to, is bound by or associates with an albumin fusion protein of the present invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0406] One of the ways in which an albumin fusion protein of the present invention can be detectably labeled is by linking the same to a reporter enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The reporter enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Reporter enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the reporter enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[0407] Albumin fusion proteins may also be radiolabelled and used in any of a variety of other immunoassays. For example, by radioactively labeling the albumin fusion proteins, it is possible to the use the albumin fusion proteins in a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[0408] Additionally, chelator molecules, are known in the art and can be used to label the Albumin fusion proteins. Chelator molecules may be attached Albumin fusion proteins of the invention to facilitate labeling said protein with metal ions including radionuclides or fluorescent labels. For example, see Subramanian, R. and Meares, C.F., "Bifunctional Chelating Agents for Radiometal-labeled monoclonal Antibodies," in *Cancer Imaging with Radiolabeled Antibodies* (D. M. Goldenberg, Ed.) Kluwer Academic Publications, Boston; Saji, H., "Targeted delivery of radiolabeled imaging and therapeutic agents: bifunctional radiopharmaceuticals." *Crit. Rev. Ther. Drug Carrier Syst. 16*:209-244 (1999); Srivastava S.C. and Mease R.C., "Progress in research on ligands, nuclides and techniques for labeling monoclonal antibodies." *Int. J. Rad. Appl. Instrum. B 18*:589-603 (1991); and Liu, S. and Edwards, D.S., "Bifunctional chelators for therapeutic lanthanide radiopharmaceuticals." *Bioconjug. Chem. 12*:7-34 (2001). Any chelator which can be covalently bound to said Albumin fusion proteins may be used according to the present invention. The chelator may further comprise a linker moiety that connects the chelating moiety to the Albumin fusion protein.

[0409] In one embodiment, the Albumin fusion protein of the invention are attached to an acyclic chelator such as diethylene triamine-N,N,N',N",N"-pentaacetic acid (DPTA), analogues of DPTA, and derivatives of DPTA. As non-limiting examples, the chelator may be 2-(p-isothiocyanatobenzyl)-6- methyldiethylenetriaminepentaacetic acid (1B4M-DPTA, also known as MX-DTPA), 2-methyl-6-(rho-nitrobenzyl)-1,4,7-triazaheptane-N,N,N',N",N"-pentaacetic acid (nitro-1B4M-DTPA or nitro-MX-DTPA); 2-(p-isothiocyanatobenzyl)-

cyclohexyldiethylenetriaminepentaacetic acid (CHX-DTPA), or N-[2-amino-3-(rho-nitrophenyl)propyl]-trans-cyclohexane-1,2-diamine-N,N',N"-pentaacetic acid (nitro-CHX-A-DTPA).

[0410] In another embodiment, the Albumin fusion protein of the invention are attached to an acyclic terpyridine chelator such as 6,6"-bis[[N,N,N",N"- tetra(carboxymethyl)amino]methyl]-4'-(3-amino-4-methoxyphenyl)-2,2':6',2 "- terpyridine (TMT-amine).

[0411] In specific embodiments, the macrocyclic chelator which is attached to the the Albumin fusion protein of the invention is 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA). In other specific embodiments, the DOTA is attached to the the Albumin fusion protein of the invention via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo *et al., Clin. Cancer Res.* *4*(10):2483-90, 1998; Peterson *et al., Bioconjug. Chem.* *10*(4):553-7, 1999; and Zimmerman *et al., Nucl. Med. Biol.* *26*(8):943-50, 1999 which are hereby incorporated by reference in their entirety. In addition, U.S. Patents 5,652,361 and 5,756,065, which disclose chelating agents that may be conjugated to antibodies, and methods for making and using them, are hereby incorporated by reference in their entireties. Though U.S. Patents 5,652,361 and 5,756,065 focus on conjugating chelating agents to antibodies, one skilled in the art could readily adapt the method disclosed therein in order to conjugate chelating agents to other polypeptides.

[0412] Bifunctional chelators based on macrocyclic ligands in which conjugation is via an activated arm, or functional group, attached to the carbon backbone of the ligand can be employed as described by M. Moi *et al., J. Amer. Chem. Soc.* *49*:2639 (1989) (2-*p*-nitrobenzyl-1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid); S. V. Deshpande *et al., J. Nucl. Med.* *31*:473 (1990); G. Ruser *et al., Bioconj. Chem.* *1*:345 (1990); C. J. Broan *et al., J. C. S. Chem. Comm.* *23*:1739 (1990); and C. J. Anderson *et al., J. Nucl. Med.* *36*:850 (1995).

[0413] In one embodiment, a macrocyclic chelator, such as polyazamacrocyclic chelators, optionally containing one or more carboxy, amino, hydroxamate, phosphonate, or phosphate groups, are attached to the Albumin fusion protein of the invention. In another embodiment, the chelator is a chelator selected from the group consisting of DOTA, analogues of DOTA, and derivatives of DOTA.

[0414] In one embodiment, suitable chelator molecules that may be attached to the the Albumin fusion protein of the invention include DOXA (1-oxa-4,7,10-triazacyclododecanetriacetic acid), NOTA (1,4,7-triazacyclononanetriacetic acid), TETA (1,4,8,11-tetraazacyclotetradecanetetraacetic acid), and THT (4'-(3-amino-4-methoxy-phenyl)-6,6"-bis(N',N'-dicarboxymethyl-*N*-methylhydra zino)-2,2':6',2"-terpyridine), and analogs and derivatives thereof. See, *e.g.*, Ohmomo *et al., J. Med. Chem.* *35*: 157-162 (1992); Kung *et al., J. Nucl. Med.* *25*: 326-332 (1984); Jurisson *et al., Chem. Rev.* *93*:1137-1156 (1993); and U.S. Patent No. 5,367,080. Other suitable chelators include chelating agents disclosed in U.S. Patent Nos. 4,647,447; 4,687,659; 4,885,363; EP-A-71564; WO89/00557; and EP-A-232751.

[0415] In another embodiment, suitable macrocyclic carboxylic acid chelators which can be used in the present invention include 1,4,7,10-tetraazacyclododecane-*N,N',N",N"'*-tetraacetic acid (DOTA); 1,4,8,12-tetraazacyclopentadecane-*N,N',N",N"'*-tetraacetic acid (15N4); 1,4,7-triazacyclononane-N,N',N"-triacetic acid (9N3); 1,5,9-triazacyclododecane-N,N',N"-triacetic acid (12N3); and 6-bromoacetamido-benzyl-1,4,8,11-tetraazacyclotetradecane- *N,N',N",N"'*-tetraacetic acid (BAT).

[0416] A preferred chelator that can be attached to the Albumin Fusion protein of the invention is α-(5-isothiocyanato- 2-methoxyphenyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, which is also known as MeO-DOTA-NCS. A salt or ester of α-(5-isothiocyanato- 2-methoxyphenyl)- 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid may also be used.

[0417] Albumin fusion proteins of the invention to which chelators such as those decribed are covalently attached may be labeled (via the coordination site of the chelator) with radionuclides that are suitable for therapeutic, diagnostic, or both therapeutic and diagnostic purposes. Examples of appropriate metals include Ag, At, Au, Bi, Cu, Ga, Ho, In, Lu, Pb, Pd, Pm, Pr, Rb, Re, Rh, Sc, Sr, Tc, Tl, Y, and Yb. Examples of the radionuclide used for diagnostic purposes are Fe, Gd, ^{111}In, ^{67}Ga, or ^{68}Ga. In another embodiment, the radionuclide used for diagnostic purposes is ^{111}In, or ^{67}Ga. Examples of the radionuclide used for therapeutic purposes are ^{166}Ho, ^{165}Dy, ^{90}Y, ^{115m}In, ^{52}Fe, or ^{72}Ga. In one embodiment, the radionuclide used for diagnostic purposes is ^{166}Ho or ^{90}Y. Examples of the radionuclides used for both therapeutic and diagnostic purposes include ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{175}Yb, or ^{47}Sc. In one embodiment, the radionuclide is ^{153}Sm, ^{177}Lu, ^{175}Yb, or ^{159}Gd.

[0418] Preferred metal radionuclides include ^{90}Y, ^{99m}Tc, ^{111}In, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{97}Ru, ^{188}Re, ^{177}Lu, ^{199}Au, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{95}Ru, ^{188}Re, ^{177}Lu, ^{199}Au, ^{203}Pb and ^{141}Ce.

[0419] In a particular embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with a metal ion selected from the group consisting of ^{90}Y, ^{111}In, ^{177}Lu, ^{166}Ho, ^{215}Bi, and ^{225}Ac.

[0420] Moreover, γ-emitting radionuclides, such as ^{99m}Tc, ^{111}In, ^{67}Ga, and ^{169}Yb have been approved or under investigation for diagnostic imaging, while β-emitters, such as ^{67}Cu, ^{111}Ag, ^{186}Re, and ^{90}Y are useful for the applications in tumor therapy. Also other useful radionuclides include γ-emitters, such as ^{99m}Tc, ^{111}In, ^{67}Ga, and ^{169}Yb, and β-emitters, such as ^{67}Cu, ^{111}Ag, ^{186}Re, ^{188}Re and ^{90}Y, as well as other radionuclides of interest such as ^{211}At, ^{212}Bi, ^{177}Lu, ^{86}Rb , ^{105}Rh, ^{153}Sm, ^{198}Au, ^{149}Pm, ^{85}Sr, ^{142}Pr, ^{214}Pb, ^{109}Pd, ^{166}Ho, ^{208}Tl, and ^{44}Sc. Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with the radionuclides described above.

[0421] In another embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with paramagnetic metal ions including ions of transition and lanthanide metal, such as metals having atomic numbers of 21-29, 42, 43, 44, or 57-71, in particular ions of Cr, V, Mn, Fe, Co, Ni, Cu, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu. The paramagnetic metals used in

compositions for magnetic resonance imaging include the elements having atomic numbers of 22 to 29, 42, 44 and 58-70.

[0422] In another embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with fluorescent metal ions including lanthanides, in particular La, Ce, Pr, Nd, Pm, Sm, Eu (e.g., ^{152}Eu), Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu.

[0423] In another embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with heavy metal-containing reporters may include atoms of Mo, Bi, Si, and W.

[0424] It is also possible to label the albumin fusion proteins with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

[0425] The albumin fusion protein can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[0426] The albumin fusion proteins can also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged albumin fusion protein is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[0427] Likewise, a bioluminescent compound may be used to label albumin fusion proteins of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Transgenic Organisms

[0428] Transgenic organisms that express the albumin fusion proteins of the invention are also included in the invention. Transgenic organisms are genetically modified organisms into which recombinant, exogenous or cloned genetic material has been transferred. Such genetic material is often referred to as a transgene. The nucleic acid sequence of the transgene may include one or more transcriptional regulatory sequences and other nucleic acid sequences such as introns, that may be necessary for optimal expression and secretion of the encoded protein. The transgene may be designed to direct the expression of the encoded protein in a manner that facilitates its recovery from the organism or from a product produced by the organism, *e.g.* from the milk, blood, urine, eggs, hair or seeds of the organism. The transgene may consist of nucleic acid sequences derived from the genome of the same species or of a different species than the species of the target animal. The transgene may be integrated either at a locus of a genome where that particular nucleic acid sequence is not otherwise normally found or at the normal locus for the transgene.

[0429] The term "germ cell line transgenic organism" refers to a transgenic organism in which the genetic alteration or genetic information was introduced into a germ line cell, thereby conferring the ability of the transgenic organism to transfer the genetic information to offspring. If such offspring in fact possess some or all of that alteration or genetic information, then they too are transgenic organisms. The alteration or genetic information may be foreign to the species of organism to which the recipient belongs, foreign only to the particular individual recipient, or may be genetic information already possessed by the recipient. In the last case, the altered or introduced gene may be expressed differently than the native gene.

[0430] A transgenic organism may be a transgenic animal or a transgenic plant. Transgenic animals can be produced by a variety of different methods including transfection, electroporation, microinjection, gene targeting in embryonic stem cells and recombinant viral and retroviral infection (*see, e.g.*, U.S. Patent No. 4,736,866; U.S. Patent No. 5,602,307; Mullins *et al.* (1993) Hypertension 22(4):630-633; Brenin *et al.* (1997) Surg. Oncol. 6(2)99-110; Tuan (ed.), *Recombinant Gene Expression Protocols*, Methods in Molecular Biology No. 62, Humana Press (1997)). The method of introduction of nucleic acid fragments into recombination competent mammalian cells can be by any method which favors co-transformation of multiple nucleic acid molecules. Detailed procedures for producing transgenic animals are readily available to one skilled in the art, including the disclosures in U.S. Patent No. 5,489,743 and U.S. Patent No. 5,602,307.

[0431] A number of recombinant or transgenic mice have been produced, including those which express an activated oncogene sequence (U.S. Patent No. 4,736,866); express simian SV40 T-antigen (U.S. Patent No. 5,728,915); lack the expression of interferon regulatory factor 1 (IRF-1) (U.S. Patent No. 5,731,490); exhibit dopaminergic dysfunction (U.S. Patent No. 5,723,719); express at least one human gene which participates in blood pressure control (U.S. Patent No. 5,731,489); display greater similarity to the conditions existing in naturally occurring Alzheimer's disease (U.S. Patent No. 5,720,936); have a reduced capacity to mediate cellular adhesion (U.S. Patent No. 5,602,307); possess a bovine growth hormone gene (Clutter *et al.* (1996) Genetics 143(4):1753-1760); or, are capable of generating a fully human antibody response (McCarthy (1997) The Lancet 349(9049):405).

[0432] While mice and rats remain the animals of choice for most transgenic experimentation, in some instances it is preferable or even necessary to use alternative animal species. Transgenic procedures have been successfully utilized in a variety of non-murine animals, including sheep, goats, pigs, dogs, cats, monkeys, chimpanzees, hamsters, rabbits, cows and guinea pigs (*see, e.g.*, Kim *et al.* (1997) Mol. Reprod. Dev.

46(4):515-526; Houdebine (1995) Reprod. Nutr. Dev. 35(6):609-617; Petters (1994) Reprod. Fertil. Dev. 6(5):643-645; Schnieke *et al.* (1997) Science 278(5346):2130-2133; and Amoah (1997) J. Animal Science 75(2):578-585).

[0433] To direct the secretion of the transgene-encoded protein of the invention into the milk of transgenic mammals, it may be put under the control of a promoter that is preferentially activated in mammary epithelial cells. Promoters that control the genes encoding milk proteins are preferred, for example the promoter for casein, beta lactoglobulin, whey acid protein, or lactalbumin (see, *e.g.*, DiTullio (1992) BioTechnology 10:74-77; Clark *et al.* (1989) BioTechnology 7:487-492; Gorton *et al.* (1987) BioTechnology 5:1183-1187; and Soulier *et al.* (1992) FEBS Letts. 297:13). The transgenic mammals of choice would produce large volumes of milk and have long lactating periods, for example goats, cows, camels or sheep.

[0434] An albumin fusion protein of the invention can also be expressed in a transgenic plant, *e.g.* a plant in which the DNA transgene is inserted into the nuclear or plastidic genome. Plant transformation procedures used to introduce foreign nucleic acids into plant cells or protoplasts are known in the art. See, in general, Methods in Enzymology Vol. 153 ("Recombinant DNA Part D") 1987, Wu and Grossman Eds., Academic Press and European Patent Application EP 693554. Methods for generation of genetically engineered plants are further described in US Patent No. 5,283,184, US Patent No. 5, 482,852, and European Patent Application EP 693 554, all of which are hereby incorporated by reference.

Pharmaceutical or Therapeutic Compositions

[0435] The albumin fusion proteins of the invention or formulations thereof may be administered by any conventional method including parenteral (*e.g.* subcutaneous or intramuscular) injection or intravenous infusion. The treatment may consist of a single dose or a plurality of doses over a period of time.

[0436] While it is possible for an albumin fusion protein of the invention to be administered alone, it is preferable to present it as a pharmaceutical formulation, together with one or more acceptable carriers. The carrier(s) must be "acceptable" in the sense of being compatible with the albumin fusion protein and not deleterious to the recipients thereof. Typically, the carriers will be water or saline which will be sterile and pyrogen free. Albumin fusion proteins of the invention are particularly well suited to formulation in aqueous carriers such as sterile pyrogen free water, saline or other isotonic solutions because of their extended shelf-life in solution. For instance, pharmaceutical compositions of the invention may be formulated well in advance in aqueous form, for instance, weeks or months or longer time periods before being dispensed.

[0437] For example, formulations containing the albumin fusion protein may be prepared taking into account the extended shelf-life of the albumin fusion protein in aqueous formulations. As discussed above, the shelf-life of many of these Therapeutic proteins are markedly increased or prolonged after fusion to HA.

[0438] In instances where aerosol administration is appropriate, the albumin fusion proteins of the invention can be formulated as aerosols using standard procedures. The term "aerosol" includes any gas-borne suspended phase of an albumin fusion protein of the instant invention which is capable of being inhaled into the bronchioles or nasal passages. Specifically, aerosol includes a gas-borne suspension of droplets of an albumin fusion protein of the instant invention, as may be produced in a metered dose inhaler or nebulizer, or in a mist sprayer. Aerosol also includes a dry powder composition of a compound of the instant invention suspended in air or other carrier gas, which may be delivered by insufflation from an inhaler device, for example. See Ganderton & Jones, *Drug Delivery to the Respiratory Tract, Ellis Horwood* (19 87); Gonda (1990) *Critical Reviews in Therapeutic Drug Carrier Systems* 6:273-313; and Raeburn *et al.*. (1992) *Pharmacol. Toxicol. Methods* 27:143-159.

[0439] The formulations of the invention are also typically non-immunogenic, in part, because of the use of the components of the albumin fusion protein being derived from the proper species. For instance, for human use, both the Therapeutic protein and albumin portions of the albumin fusion protein will typically be human. In some cases, wherein either component is non human-derived, that component may be humanized by substitution of key amino acids so that specific epitopes appear to the human immune system to be human in nature rather than foreign.

[0440] The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the albumin fusion protein with the carrier that constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0441] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation appropriate for the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampules, vials or syringes, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders. Dosage formulations may contain the Therapeutic protein portion at a lower molar concentration or lower dosage compared to the non-fused standard formulation for the Therapeutic protein given the extended serum half-life exhibited by many of the albumin fusion proteins of the invention.

[0442] As an example, when an albumin fusion protein of the invention comprises one of the proteins listed in the "Therapeutic Protein:X" column of Table 1 as one or more of the Therapeutic protein regions, the dosage form can be calculated on the basis of the potency of the albumin

fusion protein relative to the potency of the therapeutic protein alone, while taking into account the prolonged serum half-life and shelf-life of the albumin fusion proteins compared to that of native therapeutic protein. For example, if the therapeutic protein is typically administered at 0.3 to 30.0 IU/kg/week, or 0.9 to 12.0 IU/kg/week, given in three or seven divided doses for a year or more. In an albumin fusion protein consisting of full length HA fused to a therpeutic protein, an equivalent dose in terms of units would represent a greater weight of agent but the dosage frequency can be reduced, for example to twice a week, once a week or less.

[0443] Formulations or compositions of the invention may be packaged together with, or included in a kit with, instructions or a package insert referring to the extended shelf-life of the albumin fusion protein component. For instance, such instructions or package inserts may address recommended storage conditions, such as time, temperature and light, taking into account the extended or prolonged shelf-life of the albumin fusion proteins of the invention. Such instructions or package inserts may also address the particular advantages of the albumin fusion proteins of the inventions, such as the ease of storage for formulations that may require use in the field, outside of controlled hospital, clinic or office conditions. As described above, formulations of the invention may be in aqueous form and may be stored under less than ideal circumstances without significant loss of therapeutic activity.

[0444] Albumin fusion proteins of the invention can also be included in nutraceuticals. For instance, certain albumin fusion proteins of the invention may be administered in natural products, including milk or milk product obtained from a transgenic mammal which expresses albumin fusion protein. Such compositions can also include plant or plant products obtained from a transgenic plant which expresses the albumin fusion protein. The albumin fusion protein can also be provided in powder or tablet form, with or without other known additives, carriers, fillers and diluents. Nutraceuticals are described in Scott Hegenhart, *Food Product Design*, Dec. 1993.

[0445] The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of an albumin fusion protein of the invention or a polynucleotide encoding an albumin fusion protein of the invention ("albumin fusion polynucleotide") in a pharmaceutically acceptable carrier.

[0446] The albumin fusion protein and/or polynucleotide will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the albumin fusion protein and/or polynucleotide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

[0447] As a general proposition, the total pharmaceutically effective amount of the albumin fusion protein administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the albumin fusion protein is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

[0448] As noted above, the albumin fusion protein of the invention has a higher plasma stablity compared to the Therapeutic protein portion (or fragment or variant thereof) alone. This increase in plasma stability should be taken into account when determining the effective amount of the albumin fusion protein to be administered per dose and the dosing administration schedule. In particular, higher plasma stability may allow the albumin fusion protein to be administered at a lower dose at the same frequency of administrations, or alternatively, may allow the albumin fusion protein to be administered in fewer dosings. Preferably, the higher stability allows the albumin fusion protein of the invention to be administered less often in fewer dosings. More preferably, the albumin fusion protein can be administered once every two weeks. Still more preferably, the albumin fusion protein can be administered once every three, four, five, or more weeks depending on the pharmacokinetics of the albumin fusion protein. For example, as discussed above, the pharmacokinetics of an IFN-alpha-HSA fusion protein supports a dosing regimen of once every 2-4 weeks or more, and even dosing at intervals of 4 weeks or more than every 4 weeks.

[0449] Albumin fusion proteins and/or polynucleotides can be are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[0450] Albumin fusion proteins and/or polynucleotides of the invention are also suitably administered by sustained-release systems. Examples of sustained-release albumin fusion proteins and/or polynucleotides are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion. Additional examples of sustained-release albumin fusion proteins and/or polynucleotides

include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

[0451] Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

[0452] Sustained-release albumin fusion proteins and/or polynucleotides also include liposomally entrapped albumin fusion proteins and/or polynucleotides of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the albumin fusion protein and/or polynucleotide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

[0453] In yet an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

[0454] Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

[0455] For parenteral administration, in one embodiment, the albumin fusion protein and/or polynucleotide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

[0456] Generally, the formulations are prepared by contacting the albumin fusion protein and/or polynucleotide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

[0457] The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates (including, for example, Tween-20), poloxamers, or PEG.

[0458] The albumin fusion protein is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

[0459] Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Albumin fusion proteins and/or polynucleotides generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0460] Albumin fusion proteins and/or polynucleotides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous albumin fusion protein and/or polynucleotide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized albumin fusion protein and/or polynucleotide using bacteriostatic Water-for-Injection.

[0461] In a specific and preferred embodiment, the Albumin fusion protein formulations comprises 0.01 M sodium phosphate, 0.15 mM sodium chloride, 0.16 micromole sodium octanoate/milligram of fusion protein, 15 micrograms/milliliter polysorbate 80, pH 7.2. In another specific and preferred embodiment, the Albumin fusion protein formulations consists 0.01 M sodium phosphate, 0.15 mM sodium chloride, 0.16 micromole sodium octanoate/milligram of fusion protein, 15 micrograms/milliliter polysorbate 80, pH 7.2. The pH and buffer are chosen to match physiological conditions and the salt is added as a tonicifier. Sodium octanoate has been chosen due to its reported ability to increase the thermal stability of the protein in solution. Finally, polysorbate has been added as a generic surfactant, which lowers the surface tension of the solution and

lowers non-specific adsorption of the albumin fusion protein to the container closure system.

[0462] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the albumin fusion proteins and/or polynucleotides of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the albumin fusion proteins and/or polynucleotides may be employed in conjunction with other therapeutic compounds.

[0463] The albumin fusion proteins and/or polynucleotides of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable preparations of *Corynebacterium parvum*. In a specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with alum. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, *Haemophilus influenzae* B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0464] The albumin fusion proteins and/or polynucleotides of the invention may be administered alone or in combination with other therapeutic agents. Albumin fusion protein and/or polynucleotide agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0465] In one embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the compositions of the invention include, but are not limited to, heparin, low molecular weight heparin, warfarin sodium (e.g., COUMADIN®), dicumarol, 4-hydroxycoumarin, anisindione (e.g., MIRADON™), acenocoumarol (e.g., nicoumalone, SINTHROME™), indan-1,3-dione, phenprocoumon (e.g., MARCUMAR™), ethyl biscoumacetate (e.g., TROMEXAN™), and aspirin. In a specific embodiment, compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, compositions of the invention are administered in combination with heparin. In another specific embodiment, compositions of the invention are administered in combination with heparin and aspirin.

[0466] In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with thrombolytic drugs. Thrombolytic drugs that may be administered with the compositions of the invention include, but are not limited to, plasminogen, lys-plasminogen, alpha2-antiplasmin, streptokinae (e.g., KABIKINASE™), antiresplace (e.g., EMINASE™), tissue plasminogen activator (t-PA, altevase, ACTIVASE™), urokinase (e.g., ABBOKINASE™), sauruplase, (Prourokinase, single chain urokinase), and aminocaproic acid (e.g., AMICAR™). In a specific embodiment, compositions of the invention are administered in combination with tissue plasminogen activator and aspirin.

[0467] In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with antiplatelet drugs. Antiplatelet drugs that may be administered with the compositions of the invention include, but are not limited to, aspirin, dipyridamole (e.g., PERSANTINE™), and ticlopidine (e.g., TICLID™).

[0468] In specific embodiments, the use of anti-coagulants, thrombolytic and/or antiplatelet drugs in combination with albumin fusion proteins and/or polynucleotides of the invention is contemplated for the prevention, diagnosis, and/or treatment of thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the use of anticoagulants, thrombolytic drugs and/or antiplatelet drugs in combination with albumin fusion proteins and/or

polynucleotides of the invention is contemplated for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the therapeutics of the invention, alone or in combination with antiplatelet, anticoagulant, and/or thrombolytic drugs, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0469] In certain embodiments, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with albumin fusion proteins and/or polynucleotides of the invention to treat AIDS and/or to prevent or treat HIV infection.

[0470] Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott; COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); **Adefovir** (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); **TENOFOVIR™** (bis-POC PMPA, a PMPA prodrug; Gilead); **DAPD/DXG** (active metabolite of DAPD; Triangle/Abbott); **D-D4FC** (related to 3TC, with activity against AZT/3TC-resistant virus); **GW420867X** (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β-L-FD4C and β-L-FddC (WO 98/17281).

[0471] Additional NNRTIs include COACTINON™ (**Emivirine**/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); **CAPRAVIRINE™** (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830).

[0472] Additional protease inhibitors include **LOPINAVIR™** (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myres Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); **BMS 232632 (an azapeptide**; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); **VX-175/GW-433908** (phosphate prodrug of amprenavir; Vertex & Glaxo Welcome); **CGP61755** (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

[0473] Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

[0474] Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine recpetor agonists such as RANTES, SDF-1, MIP-1α, MIP-1β, etc., may also inhibit fusion.

[0475] Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; **ZINTEVIR™** (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

[0476] Additional antiretroviral agents include hydroxyurea-like compunds such as **BCX-34** (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide reductase inhibitors such as **DIDOX™** (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors sucha as VX-497 (Vertex); and mycopholic acids such as CellCept (**mycophenolate mofetil**; Roche).

[0477] Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

[0478] Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1α, MIP-1β, SDF-1α, IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN-alpha2a, IFN-alpha2b, or IFN-beta; antagonists of TNFs, NFκB, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al.*, *PNAS 94*:11567-72 (1997); Chen *et al.*, *Nat. Med. 3*:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF-α antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and α-naphthoflavone (WO 98/30213); and antioxidants such as γ-L-glutamyl-L-cysteine ethyl ester (γ-GCE; WO 99/56764).

[0479] In a further embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, remantidine, maxamine, or thymalfasin. Specifically, interferon albumin fusion protein can be administered in combination with any of these agents. Moreover, interferon alpha albumin fusion protein can also be admistered with any of these agents, and preferably, interferon alpha 2a or 2b albumin fusion protein can be administered with any of these agents. Furthermore, interferon beta albumin fusion protein can also be admistered with any of these agents. Additionally, any of the IFN hybrids albumin fusion proteins can be administered in combination with any of these agents.

[0480] In a most preferred embodiment, interferon albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, interferon alpha albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, interferon alpha 2a albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, interferon alpha 2b albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, interferon beta albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, hybrid interferon albumin fusion protein is administered in combination with ribavirin.

[0481] In other embodiments, albumin fusion proteins and/or polynucleotides of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the

invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

[0482] In a further embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

[0483] In other embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with immunestimulants. Immunostimulants that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, levamisole (e.g., ERGAMISOL™), isoprinosine (e.g. INOSIPLEX™), interferons (e.g. interferon alpha), and interleukins (e.g., IL-2).

[0484] In other embodiments, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate motefil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

[0485] In an additional embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™ (antithymocyte glubulin), and GAMIMUNE™. In a specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[0486] In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered alone or as part of a combination therapy, either in vivo to patients or in vitro to cells, for the treament of cancer. In a specific embodiment, the albumin fusion proteins, particularly IL-2-albumin fusions, are administered repeatedly during passive immunotherapy for cancer, such as adoptive cell transfer therapy for metastatic melanoma as described in Dudley *et al.* (Science Express, 19 September 2002., at www.scienceexpress.org, hereby incorporated by reference in its entirety).

[0487] In certain embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

[0488] In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0489] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include

oxo transition metal complexes.

[0490] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0491] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0492] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

[0493] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolmidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

[0494] Anti-angiogenic agents that may be administed in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositons of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositons of the invention include, but are not limited to, EMD-121974 (Merck KcgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositons of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositons of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

[0495] In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

[0496] In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

[0497] In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

[0498] In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouacil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone proprionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing horomone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

[0499] In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

[0500] In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

[0501] In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are ^{90}Y and ^{111}In.

[0502] In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with cytokines. Cytokines that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, albumin fusion proteins and/or polynucleotides of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

[0503] In one embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in

complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[0504] In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

[0505] In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[0506] In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

[0507] In certain embodiments, albumin fusion proteins and/or polynucleotides of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

[0508] In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxin, digitoxin, diliazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

[0509] In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit Na^+-K^+-$2Cl^-$ symport (e.g., furosemide, bumetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

[0510] In one embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, ^{127}I, radioactive isotopes of iodine such as ^{131}I and ^{123}I; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate),

SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T_4™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T_3™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca^{2+} channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

[0511] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or congugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

[0512] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotropic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone); bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™

(glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), ciglitazone, pioglitazone, and alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide).

[0513] In one embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN® and ESTRATAB®), estradiols (e.g., CLIMARA® and ALORA®), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN® (medroxyprogesterone), MICRONOR® (norethidrone acetate), PROMETRIUM® progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example, conjugated estrogens/medroxyprogesterone (e.g., PREMPRO™ and PREMPHASE®) and norethindrone acetate/ethinyl estsradiol (e.g., FEMHRT™).

[0514] In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin B_{12}, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PC™), hydroxocobalamin, folic acid (e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

[0515] In certain embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with agents used to treat psychiatric disorders. Psychiatric drugs that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine, divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine), antianxiety agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d-amphetamine, methylphenidate, and pemoline).

[0516] In other embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with agents used to treat neurological disorders. Neurological agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g., levodopa/carbidopa, selegiline, amantidine, bromocriptine, pergolide, ropinirole, pramipexole, benztropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, tolcapone), and ALS therapeutics (e.g. riluzole).

[0517] In another embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

[0518] In certain embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with treatments for gastrointestinal disorders. Treatments for gastrointestinal disorders that may be administered with the albumin fusion protein and/or polynucleotide of the invention include, but are not limited to, H_2 histamine receptor antagonists (e.g., TAGAMET™ (cimetidine), ZANTAC™ (ranitidine), PEPCID™ (famotidine), and AXID™ (nizatidine)); inhibitors of H^+, K^+ ATPase (e.g., PREVACID™ (lansoprazole) and PRILOSEC™ (omeprazole)); Bismuth compounds (e.g., PEPTO-BISMOL™ (bismuth subsalicylate) and DE-NOL™ (bismuth subcitrate)); various antacids; sucralfate; prostaglandin analogs (e.g. CYTOTEC™ (misoprostol)); muscarinic cholinergic antagonists; laxatives (e.g., surfactant laxatives, stimulant laxatives, saline and osmotic laxatives); antidiarrheal agents (e.g., LOMOTIL™ (diphenoxylate), MOTOFEN™ (diphenoxin), and IMODIUM™ (loperamide hydrochloride)), synthetic analogs of somatostatin such as SANDOSTATIN™ (octreotide), antiemetic agents (e.g., ZOFRAN™ (ondansetron), KYTRIL™ (granisetron hydrochloride), tropisetron, dolasetron, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, triflupromazine, domperidone, haloperidol, droperidol, trimethobenzamide, dexamethasone, methylprednisolone, dronabinol, and nabilone); D2 antagonists (e.g., metoclopramide, trimethobenzamide and chlorpromazine); bile salts; chenodeoxycholic acid; ursodeoxycholic acid; and pancreatic enzyme preparations such as pancreatin and pancrelipase.

[0519] In additional embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with

other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

[0520] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions comprising albumin fusion proteins of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Gene Therapy

[0521] Constructs encoding albumin fusion proteins of the invention can be used as a part of a gene therapy protocol to deliver therapeutically effective doses of the albumin fusion protein. A preferred approach for *in vivo* introduction of nucleic acid into a cell is by use of a viral vector containing nucleic acid, encoding an albumin fusion protein of the invention. Infection of cells with a viral vector has the advantage that a large proportion of the targeted cells can receive the nucleic acid. Additionally, molecules encoded within the viral vector, *e.g.*, by a cDNA contained in the viral vector, are expressed efficiently in cells which have taken up viral vector nucleic acid.

[0522] Retrovirus vectors and adeno-associated virus vectors can be used as a recombinant gene delivery system for the transfer of exogenous nucleic acid molecules encoding albumin fusion proteins *in vivo*. These vectors provide efficient delivery of nucleic acids into cells, and the transferred nucleic acids are stably integrated into the chromosomal DNA of the host. The development of specialized cell lines (termed "packaging cells") which produce only replication-defective retroviruses has increased the utility of retroviruses for gene therapy, and defective retroviruses are characterized for use in gene transfer for gene therapy purposes (for a review see Miller, A.D. (1990) *Blood* 76:27 1). A replication defective retrovirus can be packaged into virions which can be used to infect a target cell through the use of a helper virus by standard techniques. Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in Current Protocols in Molecular Biology, Ausubel, F.M. *et al.*, (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14 and other standard laboratory manuals.

[0523] Another viral gene delivery system useful in the present invention uses adenovirus-derived vectors. The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. See, for example, Berkner *et al.*, *BioTechniques* 6:616 (1988); Rosenfeld *et al.*, Science 252:431-434 (1991); and Rosenfeld *et al.*, *Cell* 68:143-155 (1992). Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 d1324 or other strains of adenovirus (*e.g.*, Ad2, Ad3, Ad7 etc.) are known to those skilled in the art. Recombinant adenoviruses can be advantageous in certain circumstances in that they are not capable of infecting nondividing cells and can be used to infect a wide variety of cell types, including epithelial cells (Rosenfeld *et al.*, (1992) cited supra). Furthermore, the virus particle is relatively stable and amenable to purification and concentration, and as above, can be modified so as to affect the spectrum of infectivity. Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis in situations where introduced DNA becomes integrated into the host genome (*e.g.*, retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors (Berkner *et al.*, cited supra; Haj-Ahmand *et al.*, J. Virol. 57:267 (1986)).

[0524] In another embodiment, non-viral gene delivery systems of the present invention rely on endocytic pathways for the uptake of the subject nucleotide molecule by the targeted cell. Exemplary gene delivery systems of this type include liposomal derived systems, poly-lysine conjugates, and artificial viral envelopes. In a representative embodiment, a nucleic acid molecule encoding an albumin fusion protein of the invention can be entrapped in liposomes bearing positive charges on their surface (*e.g.*, lipofectins) and (optionally) which are tagged with antibodies against cell surface antigens of the target tissue (Mizuno *et al.* (1992) *No Shinkei Geka* 20:547-5 5 1; PCT publication W091/06309; Japanese patent application 1047381; and European patent publication EP-A-43075).

[0525] Gene delivery systems for a gene encoding an albumin fusion protein of the invention can be introduced into a patient by any of a number of methods. For instance, a pharmaceutical preparation of the gene delivery system can be introduced systemically, *e.g.* by intravenous injection, and specific transduction of the protein in the target cells occurs predominantly from specificity of transfection provided by the gene delivery vehicle, cell-type or tissue-type expression due to the transcriptional regulatory sequences controlling expression of the receptor gene, or a combination thereof. In other embodiments, initial delivery of the recombinant gene is more limited with introduction into the animal being quite localized. For example, the gene delivery vehicle can be introduced by catheter (see U.S. Patent 5,328,470) or by Stereotactic injection (*e.g.* Chen *et al.* (1994) *PNAS* 91: 3 054-3 05 7). The pharmaceutical preparation of the gene therapy construct can consist essentially of the gene delivery system in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Where the albumin fusion protein can be produced intact from recombinant cells, *e.g.* retroviral vectors, the pharmaceutical preparation can comprise one or more cells which produce the albumin fusion protein.

Additional Gene Therapy Methods

[0526] Also encompassed by the invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of an albumin fusion protein of the invention. This method requires a polynucleotide which codes for an albumin fusion protein of the present

invention operatively linked to a promoter and any other genetic elements necessary for the expression of the fusion protein by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

[0527] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide encoding an albumin fusion protein of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the fusion protein of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[0528] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[0529] In one embodiment, polynucleotides encoding the albumin fusion proteins of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, polynucleotides encoding the albumin fusion proteins of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

[0530] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[0531] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the gene corresponding to the Therapeutic protein portion of the albumin fusion proteins of the invention.

[0532] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0533] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0534] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[0535] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0536] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[0537] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[0538] In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

[0539] Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[0540] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[0541] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0542] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15 degrees celcius. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[0543] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+}-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell 17:77 (1979)); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982)), which are herein incorporated by reference.

[0544] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[0545] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

[0546] In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding an albumin fusion protein of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[0547] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and $CaPO_4$ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[0548] The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding an albumin fusion protein of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express a fusion protin of the present invention.

[0549] In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses fusion protein of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al. Am. Rev. Respir. Dis.109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

[0550] Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the El region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[0551] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[0552] In certain other embodiments, the cells are engineered, ex vivo or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[0553] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a fusion protein of the invention.

[0554] Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997;

International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), which are herein encorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

[0555] Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[0556] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

[0557] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[0558] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[0559] The polynucleotide encoding an albumin fusion protein of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[0560] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[0561] A preferred method of local administration is by direct injection. Preferably, an albumin fusion protein of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[0562] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[0563] Therapeutic compositions useful in systemic administration, include fusion proteins of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising albumin fusion proteins of the invention for targeting the vehicle to a particular site.

[0564] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

[0565] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs

administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[0566] Albumin fusion proteins of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

Biological Activities

[0567] Albumin fusion proteins and/or polynucleotides encoding albumin fusion proteins of the present invention, can be used in assays to test for one or more biological activities. If an albumin fusion protein and/or polynucleotide exhibits an activity in a particular assay, it is likely that the Therapeutic protein corresponding to the fusion portein may be involved in the diseases associated with the biological activity. Thus, the fusion protein could be used to treat the associated disease.

[0568] In preferred embodiments, the present invention encompasses a method of treating a disease or disorder listed in the "Preferred Indication Y" column of Table 1 comprising administering to a patient in which such treatment, prevention or amelioration is desired an albumin fusion protein of the invention that comprises a Therapeutic protein portion corresponding to a Therapeutic protein disclosed in the "Therapeutic Protein X" column of Table 1 (in the same row as the disease or disorder to be treated is listed in the "Preferred Indication Y" column of Table 1) in an amount effective to treat, prevent or ameliorate the disease or disorder.

[0569] In a further preferred embodiment, the present invention encompasses a method of treating a disease or disorder listed for a particular Therapeutic protein in the "Preferred Indication:Y" column of Table 1 comprising administering to a patient in which such treatment, prevention or amelioration is desired an albumin fusion protein of the invention that comprises a Therapeutic protein portion corresponding to the Therapeutic protein for which the indications in the Examples are related in an amount effective to treat, prevent or ameliorate the disease or disorder.

[0570] Specifically contemplated by the present invention are albumin fusion proteins produced by a cell when encoded by the polynucleotides that encode SEQ ID NO:Y. When these polynucleotides are used to express the encoded protein from a cell, the cell's natural secretion and processing steps produces a protein that lacks the signal sequence explicitly listed in columns 4 and/or 11 of Table 2. The specific amino acid sequence of the listed signal sequence is shown in the specification or is well known in the art. Thus, most preferred embodiments of the present invention include the albumin fusion protein produced by a cell (which would lack the leader sequence shown in columns 4 and/or 11 of Table 2). Also most preferred are polypeptides comprising SEQ ID NO:Y without the specific leader sequence listed in columns 4 and/or 11 of Table 2. Compositions comprising these two preferred embodiments, including pharmaceutical compositions, are also preferred. These albumin fusion proteins are specifically contemplated to treat, prevent, or ameliorate a disease or disorder listed for a particular Therapeutic protein in the "Preferred Indication:Y" column of Table 1.

[0571] In preferred embodiments, fusion proteins of the present invention may be used in the diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders relating to diseases and disorders of the endocrine system (see, for example, "Endocrine Disorders" section below), the nervous system (see, for example, "Neurological Disorders" section below), the immune system (see, for example, "Immune Activity" section below), respiratory system (see, for example, "Respiratory Disorders" section below), cardiovascular system (see, for example, "Cardiovascular Disorders" section below), reproductive system (see, for example, "Reproductive System Disorders" section below) digestive system (see, for example, "Gastrointestinal Disorders" section below), diseases and/or disorders relating to cell proliferation (see, for example, "Hyperproliferative Disorders" section below), and/or diseases or disorders relating to the blood (see, for example, "Blood-Related Disorders" section below).

[0572] In certain embodiments, an albumin fusion protein of the present invention may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the gene corresponding to the Therapeutic protein portion of the fusion protein of the invention is expressed.

[0573] Thus, fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention are useful in the diagnosis, detection and/or treatment of diseases and/or disorders associated with activities that include, but are not limited to, prohormone activation, neurotransmitter activity, cellular signaling, cellular proliferation, cellular differentiation, and cell migration.

[0574] More generally, fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention may be useful for the diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders associated with the following systems.

Immune Activity

[0575] Albumin fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used as a marker or detector of a particular immune system disease or disorder.

[0576] In another embodiment, a fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention, may

be used to treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed.

[0577] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

[0578] In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0579] Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

[0580] In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0581] Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic alymphoplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

[0582] In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0583] In a preferred embodiment fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

[0584] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[0585] Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

[0586] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart

disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[0587] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[0588] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiotomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0589] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0590] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0591] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0592] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0593] In preferred embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a immunosuppressive agent(s).

[0594] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

[0595] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[0596] Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be

used to modulate IgE concentrations in vitro or in vivo.

[0597] Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

[0598] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myosititis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[0599] In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[0600] In other embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

[0601] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[0602] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance tumor-specific immune responses.

[0603] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles,

cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

[0604] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

[0605] In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

[0606] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

[0607] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

[0608] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

[0609] In one embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

[0610] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a stimulator of B cell responsiveness to pathogens.

[0611] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an activator of T cells.

[0612] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[0613] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to induce higher affinity antibodies.

[0614] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to increase serum immunoglobulin concentrations.

[0615] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to accelerate recovery of immunocompromised individuals.

[0616] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

[0617] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[0618] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the albumin fusion proteins of the invention

and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0619] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

[0620] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention enhance antigen presentation or antagonize antigen presentation in vitro or in vivo. Moreover, in related embodiments, this enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

[0621] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[0622] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

[0623] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodificiency.

[0624] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used in the pretreatment of bone marrow samples prior to transplant.

[0625] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

[0626] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[0627] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

[0628] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used in one or more of the applications decribed herein, as they may apply to veterinary medicine.

[0629] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

[0630] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

[0631] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

[0632] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

[0633] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the

invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

[0634] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

[0635] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to enhance or inhibit complement mediated cell lysis.

[0636] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

[0637] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

[0638] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be employed to treat adult respiratory distress syndrome (ARDS).

[0639] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to stimulate the regeneration of mucosal surfaces.

[0640] In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carnii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

[0641] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[0642] In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

[0643] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

[0644] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

[0645] In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

Blood-Related Disorders

[0646] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, fusion proteins of the

invention and/or polynucleotides encoding albumin fusion proteins of the invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

[0647] In specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, the prevention of occlusions in extrcorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0648] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed.

[0649] The fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

[0650] The fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to prevent, treat, or diagnose blood dyscrasia.

[0651] Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary siderob;astic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune helolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyldopa, dapsone, and/or sulfadrugs. Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

[0652] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to, major and minor forms of alpha-thalassemia and beta-thalassemia.

[0653] In another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophelia A or Factor VII deficiency and Christmas disease or

Factor IX deficiency, Hereditary Hemorhhagic Telangiectsia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

[0654] The effect of the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

[0655] Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

[0656] In another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leokocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

[0657] Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

[0658] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited to, lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndome, severe combined immunodeficiency, ataxia telangiectsia).

[0659] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

[0660] In another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

[0661] In yet another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphphblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukenia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

[0662] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to,

plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

[0663] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myelod metaplasia, thrombocythemia, (including both primary and seconday thrombocythemia) and chronic myelocytic leukemia.

[0664] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as a treatment prior to surgery, to increase blood cell production.

[0665] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosionophils and macrophages.

[0666] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

[0667] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to increase cytokine production.

[0668] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

Hyperproliferative Disorders

[0669] In certain embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may proliferate other cells which can inhibit the hyperproliferative disorder.

[0670] For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

[0671] Examples of hyperproliferative disorders that can be treated or detected by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0672] Similarly, other hyperproliferative disorders can also be treated or detected by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's

Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0673] In another preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

[0674] Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

[0675] Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

[0676] Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriodigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertebral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia,

periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

[0677] Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

[0678] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed.

[0679] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to, those described herein. In a further preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

[0680] Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0681] In preferred embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

[0682] Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0683] Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

[0684] Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0685] Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the

invention and/or polynucleotides encoding albumin fusion proteins of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0686] Another preferred embodiment utilizes polynucleotides encoding albumin fusion proteins of the invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

[0687] Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide encoding an albumin fusion protein of the present invention, wherein said polynucleotide represses said expression.

[0688] Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the fusion protein of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

[0689] Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

[0690] For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

[0691] The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

[0692] By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

[0693] Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

[0694] Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference).

[0695] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. These fusion protieins and/or polynucleotides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, these fusion proteins and/or polynucleotides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of these proteins, either alone or in combination with small molecule drugs or adjuviants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

[0696] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering these albumin fusion proteins and/or polynucleotides, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such thereapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

[0697] In another embodiment, the invention provides a method of delivering compositions containing the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention to targeted cells expressing the a polypeptide bound by, that binds to, or associates with an albumin fuison protein of the invention. Albumin fusion proteins of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

[0698] Albumin fusion proteins of the invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the albumin fusion proteins of the invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

Renal Disorders

[0699] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

[0700] Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis), and kidney disorders resulting form urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

[0701] In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

[0702] Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

[0703] Compositions of the invention may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Compositions of the invention may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides of the invention are described in more detail herein.

Cardiovascular Disorders

[0704] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

[0705] Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

[0706] Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

[0707] Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

[0708] Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

[0709] Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

[0710] Myocardial ischemias include, but are not limited to, coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

[0711] Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

[0712] Aneurysms include, but are not limited to, dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

[0713] Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

[0714] Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

[0715] Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat

embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include, but are not limited to, coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

[0716] Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

[0717] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Methods of delivering polynucleotides are described in more detail herein.

Respiratory Disorders

[0718] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

[0719] Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumoncoccal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

[0720] Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus. spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia* spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthsma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

Anti-Angiogenesis Activity

[0721] The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell 56*:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech. 9*:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, *333*:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res. 29*:401-411 (1985); Folkman, Advances in Cancer Research, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Opthalmol. 94*:715-743 (1982); and Folkman *et al.*, Science *221*:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest

that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science 235*:442-447 (1987).

[0722] The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)).Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention. For example, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non- small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

[0723] Within yet other aspects, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

[0724] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

[0725] For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention to a hypertrophic scar or keloid.

[0726] Within one embodiment of the present invention fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

[0727] Moreover, Ocular disorders associated with neovascularization which can be treated with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthal. 85*:704-710 (1978) and Gartner *et al.*, *Surv. Ophthal. 22*:291-312 (1978).

[0728] Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (e.g., fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis,

leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

[0729] Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

[0730] Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

[0731] Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention to the eyes, such that the formation of blood vessels is inhibited.

[0732] Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

[0733] Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreous injection and/or via intraocular implants.

[0734] Additionally, disorders which can be treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

[0735] Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

[0736] In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Albumin

fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

[0737] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

[0738] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

[0739] Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

[0740] Within one aspect of the present invention, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

[0741] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0742] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0743] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0744] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0745] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute);

Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, (1992)); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Diseases at the Cellular Level

[0746] Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Şjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0747] In preferred embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

[0748] Additional diseases or conditions associated with increased cell survival that could be treated or detected by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0749] Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognesed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

[0750] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to promote dermal reestablishment subsequent to dermal loss

[0751] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic

grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to promote skin strength and to improve the appearance of aged skin.

[0752] It is believed that fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

[0753] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may have a cytoprotective effect on the small intestine mucosa. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

[0754] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could also be used to treat gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to treat diseases associate with the under expression.

[0755] Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to prevent and heal damage to the lungs due to various pathological states. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

[0756] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

[0757] In addition, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Neural Activity and Neurological Diseases

[0758] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be

treated with the compositions of the invention (e.g., fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

[0759] In one embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

[0760] In another preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

[0761] In another preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

[0762] The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo, e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, *10*:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, *70*:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, *4*:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

[0763] In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well

as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

[0764] Further, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

[0765] Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

[0766] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to treat and/or detect neurologic diseases. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

[0767] Examples of neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

[0768] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

[0769] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

[0770] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic

diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

[0771] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include meningitis such as arachnoiditis, aseptic meningtitis such as viral meningtitis which includes lymphocytic choriomeningitis, Bacterial meningtitis which includes Haemophilus Meningtitis, Listeria Meningtitis, Meningococcal Meningtitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningtitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningtitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

[0772] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

[0773] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyloclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia,Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's

Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

[0774] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Endocrine Disorders

[0775] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

[0776] Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

[0777] Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

[0778] Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

[0779] In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

[0780] Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

[0781] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders associated with the tissue(s) in which the Therapeutic protein corresponding to the Therapeutic protein portion of the albumin protein of the invention is expressed,

Reproductive System Disorders

[0782] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

[0783] Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell

carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

[0784] Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

[0785] Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis, giant condyloma of Buscke-Lowenstein, and varrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

[0786] Moreover, diseases and/or disorders of the vas deferens include vasculititis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

[0787] Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

[0788] Further, the polynucleotides, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

[0789] Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelfus, and T-shaped uterus.

[0790] Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

[0791] Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

[0792] Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious

hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematosis, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders,and obstruction of the intestine.

[0793] Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

[0794] Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

[0795] Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

Infectious Disease

[0796] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

[0797] Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat AIDS.

[0798] Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but not limited to, the following Gram-Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., Norcardia), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthrasis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candidia, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium dificile*, *Clostridium perfringens*, *Clostridium tetani*), Coccidioides, Corynebacterium (e.g., *Corynebacterium diptheriae*), Cryptococcus, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacter (e.g. *Enterobacter aerogenes*), Enterobacteriaceae (Klebsiella, Salmonella (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), Serratia, Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., *Haemophilus influenza* type B), Helicobacter, Legionella (e.g., *Legionella pneumophila*), Leptospira, Listeria (e.g., *Listeria monocytogenes*), Mycoplasma, Mycobacterium (e.g., *Mycobacterium leprae and Mycobacterium tuberculosis)*, Vibrio (e.g., *Vibrio cholerae)*, Neisseriaceae (e.g., *Neisseria gonorrhea*, *Neisseria meningitidis*), Pasteurellacea, Proteus, Pseudomonas (e.g., *Pseudomonas aeruginosa*), Rickettsiaceae, Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.), Shigella spp., Staphylococcus (e.g., *Staphylococcus aureus*), Meningiococcus, Pneumococcus and Streptococcus (e.g., *Streptococcus pneumoniae* and Groups A, B, and C Streptococci), and Ureaplasmas. These bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye

infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, Legionella disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., mengitis types A and B), chlamydia, syphillis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections, noscomial infections. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat: tetanus, diptheria, botulism, and/or meningitis type B.

[0799] Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardias, Helminthiasis, Leishmaniasis, Schistisoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparium*, *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat, prevent, and/or diagnose malaria.

[0800] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could either be by administering an effective amount of an albumin fusion protein of the invention to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

[0801] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

[0802] Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

[0803] Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

[0804] Similarly, nerve and brain tissue could also be regenerated by using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

Gastrointestinal Disorders

[0805] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal

neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowl lymphoma)), and ulcers, such as peptic ulcers.

[0806] Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperioneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

[0807] Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata, Echinococcus granulosus, Diphyllobothrium spp.*, and *T. solium*).

[0808] Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

[0809] Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

[0810] Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

[0811] Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoin neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowl syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse,

rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

[0812] Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

Chemotaxis

[0813] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

[0814] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

[0815] It is also contemplated that fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used as an inhibitor of chemotaxis.

Binding Activity

[0816] Albumin fusion proteins of the invention may be used to screen for molecules that bind to the Therapeutic protein portion of the fusion protein or for molecules to which the Therapeutic protein portion of the fusion protein binds. The binding of the fusion protein and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the fusion protein or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

[0817] Preferably, the molecule is closely related to the natural ligand of the Therapeutic protein portion of the fusion protein of the invention, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the Therapeutic protein portion of an albumin fusion protein of the invention binds, or at least, a fragment of the receptor capable of being bound by the Therapeutic protein portion of an albumin fusion protein of the invention (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

[0818] Preferably, the screening for these molecules involves producing appropriate cells which express the albumin fusion proteins of the invention. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*.

[0819] The assay may simply test binding of a candidate compound to an albumin fusion protein of the invention, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the fusion protein.

[0820] Alternatively, the assay can be carried out using cell-free preparations, fusion protein/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing an albumin fusion protein, measuring fusion protein/molecule activity or binding, and comparing the fusion protein/molecule activity or binding to a standard.

[0821] Preferably, an ELISA assay can measure fusion protein level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure fusion protein level or activity by either binding, directly or indirectly, to the albumin fusion protein or by competing with the albumin fusion protein for a substrate.

[0822] Additionally, the receptor to which a Therapeutic protein portion of an albumin fusion protein of the invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, in cases wherein the Therapeutic protein portion of the fusion protein corresponds to FGF, expression cloning may be employed wherein polyadenylated RNA is prepared from a cell responsive to the albumin fusion protein, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the albumin fusion protein. Transfected cells which are grown on glass slides are exposed to the albumin fusion protein of the present invention, after they have been labeled. The albumin fusion proteins can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

[0823] Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

[0824] As an alternative approach for receptor identification, a labeled albumin fusion protein can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule for the Therapeutoc protein component of an albumin fusion protein of the invention, the linked material may be resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the fusion protein can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

[0825] Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the fusion protein, and/or Therapeutic protein portion or albumin component of an albumin fusion protein of the present invention, thereby effectively generating agonists and antagonists of an albumin fusion protein of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al., Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al., J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides encoding albumin fusion proteins of the invention and thus, the albumin fusion proteins encoded thereby, may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides encoding albumin fusion proteins of the invention and thus, the albumin fusion proteins encoded thereby, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of an albumin fusion protein of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

[0826] Other preferred fragments are biologically active fragments of the Therapeutic protein portion and/or albumin component of the albumin fusion proteins of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of a Therapeutic protein portion and/or albumin component of the albumin fusion proteins of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0827] Additionally, this invention provides a method of screening compounds to identify those which modulate the action of an albumin fusion protein of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, an albumin fusion protein of the present invention, and the compound to be screened and ^{3}[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of ^{3}[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of ^{3}[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

[0828] In another method, a mammalian cell or membrane preparation expressing a receptor for the Therapeutic protien component of a fusion protine of the invention is incubated with a labeled fusion protein of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second

messenger response is measured to determine if the compound is a potential fusion protein. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

[0829] All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the fusion protein/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the albumin fusion proteins of the invention from suitably manipulated cells or tissues.

[0830] Therefore, the invention includes a method of identifying compounds which bind to an albumin fusion protein of the invention comprising the steps of: (a) incubating a candidate binding compound with an albumin fusion protein of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with an albumin fusion protein of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the fusion protein has been altered.

Targeted Delivery

[0831] In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a component of an albumin fusion protein of the invention.

[0832] As discussed herein, fusion proteins of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering fusion proteins of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a Therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0833] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering an albumin fusion protein of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

[0834] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

[0835] Further contemplated is the use of the albumin fusion proteins of the present invention, or the polynucleotides encoding these fusion proteins, to screen for molecules which modify the activities of the albumin fusion protein of the present invention or proteins corresponding to the Therapeutic protein portion of the albumin fusion protein. Such a method would include contacting the fusion protein with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of the fusion protein following binding.

[0836] This invention is particularly useful for screening therapeutic compounds by using the albumin fusion proteins of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The albumin fusion protein employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the albumin fusion protein. Drugs are screened against such transformed cells or supernatants obtained from culturing such cells, in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and an albumin fusion protein of the present invention.

[0837] Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the albumin fusion proteins of the present invention. These methods comprise contacting such an agent with an albumin fusion protein of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the albumin fusion protein or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the albumin fusion protein of the present invention.

[0838] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to an albumin

fusion protein of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with an albumin fusion protein of the present invention and washed. Bound peptides are then detected by methods well known in the art. Purified albumin fusion protein may be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[0839] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding an albumin fusion protein of the present invention specifically compete with a test compound for binding to the albumin fusion protein or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with an albumin fusion protein of the invention.

Binding Peptides and Other Molecules

[0840] The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind albumin fusion proteins of the invention, and the binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the albumin fusion proteins of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

[0841] This method comprises the steps of: contacting an albumin fusion protein of the invention with a plurality of molecules; and identifying a molecule that binds the albumin fusion protein.

[0842] The step of contacting the albumin fusion protein of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the albumin fusion protein on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized albumin fusion protein of the invention. The molecules having a selective affinity for the albumin fusion protein can then be purified by affinity selection. The nature of the solid support, process for attachment of the albumin fusion protein to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

[0843] Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by an albumin fusion protein of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the albumin fusion protein and the individual clone. Prior to contacting the albumin fusion protein with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for an albumin fusion protein of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for an albumin fusion protein of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

[0844] In certain situations, it may be desirable to wash away any unbound polypeptides from a mixture of an albumin fusion protein of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the albumin fusion protein of the invention or the plurality of polypeptides are bound to a solid support.

[0845] The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind an albumin fusion protein of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and *in vitro* translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., Science 251:767-773 (1991); Houghten et al., Nature 354:84-86 (1991); Lam et al., Nature 354:82-84 (1991); Medynski, Bio/Technology 12:709-710 (1994); Gallop et al., J. Medicinal Chemistry 37(9):1233-1251 (1994); Ohlmeyer et al., Proc. Natl. Acad. Sci. USA 90:10922-10926 (1993); Erb et al., Proc. Natl. Acad. Sci. USA 91:11422-11426 (1994); Houghten et al., Biotechniques 13:412 (1992); Jayawickreme et al., Proc. Natl. Acad. Sci. USA 91:1614-1618 (1994); Salmon et al., Proc. Natl. Acad. Sci. USA 90:11708-11712 (1993); PCT Publication No. WO 93/20242; and Brenner and Lerner, Proc. Natl. Acad. Sci. USA 89:5381-5383 (1992).

[0846] Examples of phage display libraries are described in Scott et al., Science 249:386-390 (1990); Devlin et al., Science, 249:404-406 (1990); Christian et al., 1992, J. Mol. Biol. 227:711-718 1992); Lenstra, J. Immunol. Meth. 152:149-157 (1992); Kay et al., Gene 128:59-65 (1993); and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

[0847] In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., Proc. Natl. Acad. Sci. USA 91:9022-9026 (1994).

[0848] By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., Proc. Natl. Acad. Sci. USA 91:4708-4712 (1994)) can be adapted for use. Peptoid libraries (Simon et al., Proc. Natl. Acad. Sci. USA 89:9367-9371 (1992)) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (Proc. Natl. Acad. Sci. USA 91:11138-11142 (1994)).

[0849] The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke (Bio/Technology 13:351-360 (1995) list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

[0850] Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

[0851] Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

[0852] Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley et al., Adv. Exp. Med. Biol. 251:215-218 (1989); Scott et al,. Science 249:386-390 (1990); Fowlkes et al., BioTechniques 13:422-427 (1992); Oldenburg et al., Proc. Natl. Acad. Sci. USA 89:5393-5397 (1992); Yu et al., Cell 76:933-945 (1994); Staudt et al., Science 241:577-580 (1988); Bock et al., Nature 355:564-566 (1992); Tuerk et al., Proc. Natl. Acad. Sci. USA 89:6988-6992 (1992); Ellington et al., Nature 355:850-852 (1992); U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar et al., Science 263:671-673 (1993); and PCT Publication No. WO 94/18318.

[0853] In a specific embodiment, screening to identify a molecule that binds an albumin fusion protein of the invention can be carried out by contacting the library members with an albumin fusion protein of the invention immobilized on a solid phase and harvesting those library members that bind to the albumin fusion protein. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley et al., Gene 73:305-318 (1988); Fowlkes et al., BioTechniques 13:422-427 (1992); PCT Publication No. WO 94/18318; and in references cited herein.

[0854] In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields et al., Nature 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA 88:9578-9582 (1991) can be used to identify molecules that specifically bind to polypeptides of the invention.

[0855] Where the binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

[0856] Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

[0857] As mentioned above, in the case of a binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

[0858] The selected binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Other Activities

[0859] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

[0860] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

[0861] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

[0862] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

[0863] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed for preventing hair loss. Along the same lines, an albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

[0864] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

[0865] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

[0866] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, an albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

[0867] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

[0868] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

[0869] The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

[0870] Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

[0871] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the alterations detected in the present invention and practice the claimed methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

EXAMPLES

EXAMPLE 1: Generation of pScNHSA and pScCHSA.

[0872] The vectors pScNHSA (ATCC Deposit No. PTA-3279) and pScCHSA (ATCC Deposit No. PTA-3276) are derivatives of pPPC0005 (ATCC Deposit No. PTA-3278) and are used as cloning vectors into which polynucleotides encoding a therapeutic protein or fragment or variant thereof is inserted adjacent to and in translation frame with polynucleotides encoding human serum albumin "HSA". pScCHSA may be used for generating Therapeutic protein-HSA fusions, while pScNHSA may be used to generate HSA-Therapeutic protein fusions.

Generation of pScCHSA: albumin fusion with the albumin moiety C-terminal to the therapeutic portion.

[0873] A vector to facilitate cloning DNA encoding a Therapeutic protein N-terminal to DNA encoding the mature albumin protein was made by altering the nucleic acid sequence that encodes the chimeric HSA signal peptide in pPPC0005 to include the *Xho* I and *Cla* I restriction sites.

[0874] First, the *Xho* I and *Cla* I sites inherent to pPPC0005 (located 3' of the ADH1 terminator sequence) were eliminated by digesting pPPC0005 with *Xho* I and *Cla* I, filling in the sticky ends with T4 DNA polymerase, and religating the blunt ends to create pPPC0006.

[0875] Second, the *Xho* I and *Cla* I restriction sites were engineered into the nucleic acid sequence that encodes the signal peptide of HSA (a chimera of the HSA leader and a kex2 site from mating factor alpha, "MAF") in pPPC0006 using two rounds of PCR. In the first round of PCR, amplification with primers shown as SEQ ID NO:36 and SEQ ID NO:37 was performed. The primer whose sequence is shown as SEQ ID NO:36 comprises a nucleic acid sequence that encodes part of the signal peptide sequence of HSA, a kex2 site from the mating factor alpha leader sequence, and part of the amino-terminus of the mature form of HSA. Four point mutations were introduced in the sequence, creating the *Xho* I and *Cla* I sites found at the junction of the chimeric signal peptide and the mature form of HSA. These four mutations are underlined in the sequence shown below. In pPPC0005 the nucleotides at these four positions from 5' to 3' are T, G, T, and G.

5'-GCCTCGAGAAAAGAGATGCACACAAGAGTGAGGTTGCTCATCGATTTAAAGATTTGGG-3' (SEQ ID NO:36) and

5'-AATCGATGAGCAACCTCACTCTTGTGTGCATCTCTTTTCTCGAGGCTCCTGGAATAAGC-3' (SEQ ID NO:37). A second round of PCR was then performed with an upstream flanking primer, 5'-TACAAACTTAAGAGTCCAATTAGC-3' (SEQ ID NO:38) and a downstream flanking primer 5'-CACTTCTCTAGAGTGGTTTCATATGTCTT-3' (SEQ ID NO:39). The resulting PCR product was then purified and digested with *Afl* II and *Xba* I and ligated into the same sites in pPPC0006 creating pScCHSA. The resulting plasmid has *Xho* I and *Cla* I sites engineered into the signal sequence. The presence of the *Xho* I site creates a single amino acid change in the end of the signal sequence from LDKR to LEKR. The D to E change will not be present in the final albumin fusion protein expression plasmid when a nucleic acid sequence comprising a polynucleotide encoding the Therapeutic portion of the albumin fusion protein with a 5' *Sal* I site (which is compatible with the *Xho* I site) and a 3' *Cla* I site is ligated into the *Xho* I and *Cla* I sites of pScCHSA. Ligation of *Sal* I to *Xho* I restores the original amino acid sequence of the signal peptide sequence. DNA encoding the Therapeutic portion of the albumin fusion protein may be inserted after the Kex2 site (Kex2 cleaves after the dibasic amino acid sequence KR at the end of the signal peptide) and prior to the *Cla* I site.

Generation of pScNHSA: albumin fusion with the albumin moiety N-terminal to the therapeutic portion.

[0876] A vector to facilitate cloning DNA encoding a Therapeutic protein portion C-terminal to DNA encoding the mature albumin protein, was made by adding three, eight-base-pair restriction sites to pScCHSA. The *Asc* I, *Fse* I, and *Pme* I restriction sites were added in between the *Bsu36* I and *Hind* III sites at the end of the nucleic acid sequence encoding the mature HSA protein. This was accomplished through the use of two complementary synthetic primers containing the *Asc* I, *Fse* I, and *Pme* I restriction sites underlined (SEQ ID NO:40 and SEQ ID NO:41).

5'-AAGCTGCCTTAGGCTTATAATAAGGCGCGCCGGCCGGCCGTTTAAACTAAGCTTAATTCT-3' (SEQ ID NO:40) and

5-AGAATTAAGCTTAGTTTAAACGGCCGGCCGGCGCGCCTTATTATAAGCCTAAGGCAGCTT-3' (SEQ ID NO:41). These primers were annealed and digested with *Bsu36* I and *Hind* III and ligated into the same sites in pScCHSA creating pScNHSA.

EXAMPLE 2: General Construct Generation for Yeast Transformation.

[0877] The vectors pScNHSA and pScCHSA may be used as cloning vectors into which polynucleotides encoding a therapeutic protein or fragment or variant thereof is inserted adjacent to polynucleotides encoding mature human serum albumin "HSA". pScCHSA is used for generating Therapeutic protein-HSA fusions, while pScNHSA may be used to generate HSA-Therapeutic protein fusions.

Generation of albumin fusion constructs comprising HSA-Therapeutic protein fusion products.

[0878] DNA encoding a Therapeutic protein (e.g., sequences shown in SEQ ID NO:X or known in the art) may be PCR amplified using the primers which facilitate the generation of a fusion construct (e.g., by adding restriction sites, encoding seamless fusions, encoding linker sequences, etc.) For example, one skilled in the art could design a 5' primer that adds polynucleotides encoding the last four amino acids of the mature form of HSA (and containing the *Bsu*36I site) onto the 5' end of DNA encoding a Therapeutic protein; and a 3' primer that adds a STOP codon and appropriate cloning sites onto the 3' end of the Therapeutic protein coding sequence. For instance, the forward primer used to amplify DNA encoding a Therapeutic protein might have the sequence, 5'-aagctGCCTTAGGCTTA$(N)_{15}$-3' (SEQ ID NO:42) where the underlined sequence is a *Bsu*36I site, the upper case nucleotides encode the last four amino acids of the mature HSA protein (ALGL), and $(N)_{15}$ is identical to the first 15 nucleotides encoding the Therapetic protein of interest. Similarly, the reverse primer used to amplify DNA encoding a Therapeutic protein might have the sequence, 5'-GCGCGC*GTTTAAAC*GGCCGGCCGGCGCGCC$\boxed{\text{TTATTA}}$$(N)_{15}$-3' (SEQ ID NO:43) where the italicized sequence is a *Pme* I site, the double underlined sequence is an *Fse* I site, the singly underlined sequence is an *Asc* I site, the boxed nucleotides are the reverse complement of two tandem stop codons, and $(N)_{15}$ is identical to the reverse complement of the last 15 nucleotides encoding the Therapeutic protein of interest. Once the PCR product is amplified it may be cut with *Bsu*36I and one of (*Asc* I, *Fse* I, or *Pme* I) and ligated into pScNHSA.

[0879] The presence of the *Xho* I site in the HSA chimeric leader sequence creates a single amino acid change in the end of the chimeric signal sequence, i.e. the HSA-kex2 signal sequence, from LDKR (SEQ ID NO:44) to LEKR (SEQ ID NO:45).

Generation of albumin fusion constructs comprising gene-HSA fusion products.

[0880] Similar to the method described above, DNA encoding a Therapeutic protein may be PCR amplified using the following primers: A 5' primer that adds polynucleotides containing a *SalI* site and encoding the last three amino acids of the HSA leader sequence, DKR, onto the 5' end of DNA encoding a Therapeutic protein; and a 3' primer that adds polynucleotides encoding the first few amino acids of the mature HSA containing a

Cla I site onto the 3' end of DNA encoding a Therapeutic protein. For instance, the forward primer used to amplify the DNA encoding a Therapeutic protein might have the sequence, 5'-aggagcgtcGACAAAAGA(N)$_{15}$-3' (SEQ ID NO:46) where the underlined sequence is a *Sal* I site, the upper case nucleotides encode the last three amino acids of the HSA leader sequence (DKR), and (N)$_{15}$ is identical to the first 15 nucleotides encoding the Therapetic protein of interest. Similarly, the reverse primer used to amplify the DNA encoding a Therapeutic protein might have the sequence, 5'-CTTTAA*ATCGAT*GAGCAACCTCACTCTTGTGTGCATC(N)$_{15}$-3'(SEQ ID NO:47) where the italicized sequence is a *Cla* I site, the underlined nucleotides are the reverse complement of the DNA encoding the first 9 amino acids of the mature form of HSA (DAHKSEVAH, SEQ ID NO:48), and (N)$_{15}$ is identical to the reverse complement of the last 15 nucleotides encoding the Therapeutic protein of interest. Once the PCR product is amplified it may be cut with *Sal* I and *Cla* I and ligated into pScCHSA digested with *Xho* I and *Cla* I. A different signal or leader sequence may be desired, for example, invertase "INV" (Swiss-Prot Accession P00724), mating factor alpha "MAF" (Genbank Accession AAA18405), MPIF (Geneseq AAF82936), Fibulin B (Swiss-Prot Accession P23142), Clusterin (Swiss-Prot Accession P10909), Insulin-Like Growth Factor- Binding Protein 4 (Swiss-Prot Accession P22692), and permutations of the HSA leader sequence can be subcloned into the appropriate vector by means of standard methods known in the art.

Generation of albumin fusion construct compatible for expression in yeast S. cerevisiae.

[0881] The *Not* I fragment containing the DNA encoding either an N-terminal or C-terminal albumin fusion protein generated from pScNHSA or pScCHSA may then be cloned into the *Not* I site of pSAC35 which has a LEU2 selectable marker. The resulting vector is then used in transformation of a yeast *S. cerevisiae* expression system.

EXAMPLE 3: General Expression in Yeast S. cerevisiae.

[0882] An expression vector compatible with yeast expression can be transformed into yeast *S. cerevisiae* by lithium acetate transformation, electroporation, or other methods known in the art and or as described in part in Sambrook, Fritsch, and Maniatis. 1989. "Molecular Cloning: A Laboratory Manual, 2nd edition", volumes 1-3, and in Ausubel et al. 2000. Massachusetts General Hospital and Harvard Medical School "Current Protocols in Molecular Biology", volumes 1-4. The expression vectors are introduced into *S. cerevisiae* strains DXY1, D88, or BXP10 by transformation, individual transformants can be grown, for example, for 3 days at 30°C in 10 mL YEPD (1% w/v yeast extract, 2 % w/v, peptone, 2 % w/v, dextrose), and cells can be collected at stationary phase after 60 hours of growth. Supernatants are collected by clarifying cells at 3000g for 10 minutes.

[0883] pSAC35 (Sleep et al., 1990, Biotechnology 8:42 and see Figure 3) comprises, in addition to the LEU2 selectable marker, the entire yeast 2 µm plasmid to provide replication functions, the PRB1 promoter, and the ADH1 termination signal.

EXAMPLE 4: General Purification of an Albumin Fusion Protein Expressed from an Albumin Fusion in Yeast S. cerevisiae.

[0884] In preferred embodiments, albumin fusion proteins of the invention comprise the mature form of HSA fused to either the N- or C-terminus of the mature form of a therapeutic protein or portions thereof (e.g., the mature form of a therapeutic protein listed in Table 1, or the mature form of a therapeutic protein shown in Table 2 as SEQ ID NO:Z). In one embodiment of the invention, albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature albumin fusion protein is secreted directly into the culture medium. Albumin fusion proteins of the invention preferably comprise heterologous signal sequences (e.g., the non-native signal sequence of a particular therapeutic protein) including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. Especially preferred as those signal sequence listed in Table 2 and/or the signal sequence listed in the "Expression of Fusion Proteins" and/or "Additional Methods of Recombinant and Synthetic Production of Albumin Fusion Proteins" section of the specification, above. In preferred embodiments, the fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

[0885] Albumin fusion proteins expressed in yeast as described above can be purified on a small-scale over a Dyax peptide affinity column as follows. Supernatants from yeast expressing an albumin fusion protein is diafiltrated against 3 mM phosphate buffer pH 6.2, 20 mM NaCl and 0.01% Tween 20 to reduce the volume and to remove the pigments. The solution is then filtered through a 0.22 µm device. The filtrate is loaded onto a Dyax peptide affinity column. The column is eluted with 100 mM Tris/HCl, pH 8.2 buffer. The peak fractions containing protein are collected and analyzed on SDS-PAGE after concentrating 5-fold.

[0886] For large scale purification, the following method can be utilized. The supernatant in excess of 2 L is diafiltered and concentrated to 500 mL in 20 mM Tris/HCl pH 8.0. The concentrated protein solution is loaded onto a pre-equilibrated 50 mL DEAE-Sepharose Fast Flow column, the column is washed, and the protein is eluted with a linear gradient of NaCl from 0 to 0.4 M NaCl in 20 mM Tris/HCl, pH 8.0. Those fractions containing the protein are pooled, adjusted to pH 6.8 with 0.5 M sodium phosphate (NaH_2PO_4). A final concentration of 0.9 M $(NH_4)_2SO_4$ is added to the protein solution and the whole solution is loaded onto a pre-equilibrated 50 mL Butyl650S column. The protein is eluted with a linear gradient of ammonium sulfate (0.9 to 0 M $(NH_4)_2SO_4$). Those fractions with the albumin fusion are again pooled, diafiltered against 10 mM Na_2HPO_4/citric acid buffer pH 5.75, and loaded onto a 50 mL pre-equilibrated SP-Sepharose Fast Flow column. The protein is eluted with a NaCl

linear gradient from 0 to 0.5 M. The fractions containing the protein of interest are combined, the buffer is changed to 10 mM Na_2HPO_4/citric acid pH 6.25 with an Amicon concentrator, the conductivity is < 2.5 mS/cm. This protein solution is loaded onto a 15 mL pre-equilibrated Q-Sepharose high performance column, the column is washed, and the protein is eluted with a NaCl linear gradient from 0 to 0.15 M NaCl. The purified protein can then be formulated into a specific buffer composition by buffer exchange.

EXAMPLE 5: General Construct Generation for Mammalian Cell Transfection.

Generation of albumin fusion construct compatible for expression in mammalian cell-lines.

[0887] Albumin fusion constructs can be generated in expression vectors for use in mammalian cell culture systems. DNA encoding a therapeutic protein can be cloned N-terminus or C-terminus to HSA in a mammalian expression vector by standard methods known in the art (e.g., PCR amplification, restriction digestion, and ligation). Once the expression vector has been constructed, transfection into a mammalian expression system can proceed. Suitable vectors are known in the art including, but not limited to, for example, the pC4 vector, and/or vectors available from Lonza Biologics, Inc. (Portsmouth, NH).

[0888] The DNA encoding human serum albumin has been cloned into the pC4 vector which is suitable for mammalian culture systems, creating plasmid pC4:HSA (ATCC Deposit # PTA-3277). This vector has a DiHydroFolate Reductase, "DHFR", gene that will allow for selection in the presence of methotrexate.

[0889] The pC4:HSA vector is suitable for expression of albumin fusion proteins in CHO cells. For expression, in other mammalian cell culture systems, it may be desirable to subclone a fragment comprising, or alternatively consisting of, DNA which encodes for an albumin fusion protein into an alternative expression vector. For example, a fragment comprising, or alternatively consisting, of DNA which encodes for a mature albumin fusion protein may be subcloned into another expression vector including, but not limited to, any of the mammalian expression vectors described herein.

[0890] In a preferred embodiment, DNA encoding an albumin fusion construct is subcloned into vectors provided by Lonza Biologics, Inc. (Portsmouth, NH) by procedures known in the art for expression in NS0 cells.

Generation of albumin fusion constructs comprising HSA-Therapeutic Protein fusion products.

[0891] Using pC4:HSA (ATCC Deposit # PTA-3277), albumin fusion constructs can be generated in which the Therapeutic protein portion is C terminal to the mature albumin sequence. For example, one can clone DNA encoding a Therapeutic protein of fragment or variant thereof between the *Bsu* 36I and *Asc* I restriction sites of the vector. When cloning into the *Bsu* 36I and *Asc* I, the same primer design used to clone into the yeast vector system (SEQ ID NO:42 and 43) may be employed (see Example 2).

Generation of albumin fusion constructs comprising gene-HSA fusion products.

[0892] Using pC4:HSA (ATCC Deposit # PTA-3277), albumin fusion constructs can be generated in which a Therapeutic protein portion is cloned N terminal to the mature albumin sequence. For example, one can clone DNA encoding a Therapeutic protein that has its own signal sequence between the *Bam* HI (or *Hind* III) and *Cla* I sites of pC4:HSA. When cloning into either the *Bam* HI or *Hind* III site, it is preferrable to include a Kozak sequence (CCGCCACCATG, SEQ ID NO:49) prior to the translational start codon of the DNA encoding the Therapeutic protein. If a Therapeutic protein does not have a signal sequence, DNA encoding that Therapeutic protein may be cloned in between the *Xho* I and *Cla* I sites of pC4:HSA. When using the *Xho* I site, the following 5' (SEQ ID NO:50) and 3' (SEQ ID NO:51) exemplary PCR primers may be used:

5'-CCGCCGCTCGAGGGGTGTGTTTCGTCGA$(N)_{18}$-3' (SEQ ID NO: 50)

5'-AGTCCCATCGATGAGCAACCTCACTCTTGTGTGCATC$(N)_{18}$-3' (SEQ ID NO:51)

[0893] In the 5' primer (SEQ ID NO:50), the underlined sequence is a *Xho* I site; and the *Xho* I site and the DNA following the *Xho* I site code for the last seven amino acids of the leader sequence of natural human serum albumin. In SEQ ID NO:50, "$(N)_{18}$" is DNA identical to the first 18 nucleotides encoding the Therapeutic protein of interest. In the 3' primer (SEQ ID NO:51), the underlined sequence is a *Cla* I site; and the *Cla* I site and the DNA following it are the reverse complement of the DNA encoding the first 10 amino acids of the mature HSA protein (SEQ ID NO:1). In SEQ ID NO:51 "$(N)_{18}$" is the reverse complement of DNA encoding the last 18 nucleotides encoding the Therapeutic protein of interest. Using these two primers, one may PCR amplify the Therapeutic protein of interest, purify the PCR product, digest it with *Xho* I and *Cla* I restriction enzymes and clone it into the *Xho* I and *Cla* I sites in the pC4:HSA vector.

[0894] If an alternative leader sequence is desired, the native albumin leader sequence can be replaced with the chimeric albumin leader, i.e., the HSA-kex2 signal peptide, or an alternative leader by standard methods known in the art. (For example, one skilled in the art could routinely PCR amplify an alternate leader and subclone the PCR product into an albumin fusion construct in place of the albumin leader while maintaining the reading frame).

EXAMPLE 6: General Expression in Mammalian Cell-Lines.

[0895] An albumin fusion construct generated in an expression vector compatible with expression in mammalian cell-lines can be transfected into appropriate cell-lines by calcium phosphate precipitation, lipofectamine, electroporation, or other transfection methods known in the art and/or as described in Sambrook, Fritsch, and Maniatis. 1989. "Molecular Cloning: A Laboratory Manual, 2nd edition" and in Ausubel et al. 2000. Massachusetts General Hospital and Harvard Medical School "Current Protocols in Molecular Biology", volumes 1-4. The transfected cells are then

selected for by the presence of a selecting agent determined by the selectable marker in the expression vector.

[0896] The pC4 expression vector (ATCC Accession No. 209646) is a derivative of the plasmid pSV2-DHFR (ATCC Accession No. 37146). pC4 contains the strong promoter Long Terminal Repeats "LTR" of the Rous Sarcoma Virus (Cullen et al., March 1985, Molecular and Cellular Biology, 438-447) and a fragment of the CytoMegaloVirus "CMV"-enhancer (Boshart et al., 1985, Cell 41: 521-530). The vector also contains the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary "CHO" cells or other cell-lines lacking an active DHFR gene are used for transfection. Transfection of an albumin fusion construct in pC4 into CHO cells by methods known in the art will allow for the expression of the albumin fusion protein in CHO cells, followed by leader sequence cleavage, and secretion into the supernatant. The albumin fusion protein is then further purified from the supernatant.

[0897] The pEE12.1 expression vector is provided by Lonza Biologics, Inc. (Portsmouth, NH) and is a derivative of pEE6 (Stephens and Cockett, 1989, Nucl. Acids Res. 17: 7110). This vector comprises a promoter, enhancer and complete 5'-untranslated region of the Major Immediate Early gene of the human CytoMegaloVirus, "hCMV-MIE" (International Publication # WO89/01036), upstream of a sequence of interest, and a Glutamine Synthetase gene (Murphy et al., 1991, Biochem J. 227: 277-279; Bebbington et al., 1992, Bio/Technology 10:169-175; US patent US 5,122,464) for purposes of selection of transfected cells in selective methionine sulphoximine containing medium. Transfection of albumin fusion constructs made in pEE12.1 into NS0 cells (International Publication # WO86/05807) by methods known in the art will allow for the expression of the albumin fusion protein in NS0 cells, followed by leader sequence cleavage, and secretion into the supernatant. The albumin fusion protein is then further purified from the supernatant using techniques described herein or otherwise known in the art.

[0898] Expression of an albumin fusion protein may be analyzed, for example, by SDS-PAGE and Western blot, reversed phase HPLC analysis, or other methods known in the art.

[0899] Stable CHO and NS0 cell-lines transfected with albumin fusion constructs are generated by methods known in the art (e.g., lipofectamine transfection) and selected, for example, with 100 nM methotrexate for vectors having the DiHydroFolate Reductase 'DHFR' gene as a selectable marker or through growth in the absence of glutamine. Expression levels can be examined for example, by immunoblotting, primarily, with an anti-HSA serum as the primary antibody, or, secondarily, with serum containing antibodies directed to the Therapeutic protein portion of a given albumin fusion protein as the primary antibody.

[0900] Expression levels are examined by immunoblot detection with anti-HSA serum as the primary antibody. The specific productivity rates are determined via ELISA in which the capture antibody can be a monoclonal antibody towards the therapeutic protein portion of the albumin fusion and the detecting antibody can be the monoclonal anti-HSA-biotinylated antibody *(or vice versa)*, followed by horseradish peroxidase/streptavidin binding and analysis according to the manufacturer's protocol.

EXAMPLE 7: Expression of an Albumin Fusion Protein in Mammalian Cells.

[0901] The albumin fusion proteins of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

[0902] Suitable expression vectors for use in practicing the present invention include, for example, vectors such as, pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, but are not limited to, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

[0903] Alternatively, the albumin fusion protein can be expressed in stable cell lines containing the polynucleotide encoding the albumin fusion protein integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

[0904] The transfected polynucleotide encoding the fusion protein can also be amplified to express large amounts of the encoded fusion protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin et al., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page et al., Biotechnology 9:64-68 (1991)). Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

[0905] Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology,

438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

[0906] Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

[0907] A polynucleotide encoding an albumin fusion protein of the present invention is generated using techniques known in the art and this polynucleotide is amplified using PCR technology known in the art. If a naturally occurring signal sequence is used to produce the fusion protein of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

[0908] The amplified fragment encoding the fusion protein of the invention is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[0909] The amplified fragment encoding the albumin fusion protein of the invention is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

[0910] Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 μg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μM. Expression of the desired fusion protein is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

EXAMPLE 8: General Purification of an Albumin Fusion Protein Expressed from an Albumin Fusion Construct in Mammalian Cell-lines.

[0911] In preferred embodiments, albumin fusion proteins of the invention comprise the mature form of HSA fused to either the N- or C-terminus of the mature form of a therapeutic protein or portions thereof (e.g., the mature form of a therapeutic protein listed in Table 1, or the mature form of a therapeutic protein shown in Table 2 as SEQ ID NO:Z). In one embodiment of the invention, albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature albumin fusion protein is secreted directly into the culture medium. Albumin fusion proteins of the invention preferably comprise heterologous signal sequences (e.g., the non-native signal sequence of a particular therapeutic protein) including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. Especially preferred as those signal sequence listed in Table 2 and/or the signal sequence listed in the "Expression of Fusion Proteins" and/or "Additional Methods of Recombinant and Synthetic Production of Albumin Fusion Proteins" section of the specification, above. In preferred embodiments, the fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

[0912] Albumin fusion proteins from mammalian cell-line supernatants are purified according to different protocols depending on the expression system used.

Purification from CHO and 293T cell-lines.

[0913] Purification of an albumin fusion protein from CHO cell supernatant or from transiently transfected 293T cell supernatant may involve initial capture with an anionic HQ resin using a sodium phosphate buffer and a phosphate gradient elution, followed by affinity chromatography on a Blue Sepharose FF column using a salt gradient elution. Blue Sepharose FF removes the main BSA/fetuin contaminants. Further purification over the Poros PI 50 resin with a phosphate gradient may remove and lower endotoxin contamination as well as concentrate the albumin fusion protein.

Purification from NS0 cell-line.

[0914] Purification of an albumin-fusion protein from NS0 cell supernatant may involve Q-Sepharose anion exchange chromatography, followed by SP-sepharose purification with a step elution, followed by Phenyl-650M purification with a step elution, and, ultimately, diafiltration.

[0915] The purified protein may then be formulated by buffer exchange.

EXAMPLE 9: Bacterial Expression of an Albumin Fusion Protein.

[0916] A polynucleotide encoding an albumin fusion protein of the present invention comprising a bacterial signal sequence is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, to synthesize insertion fragments. The primers used to amplify the polynucleotide encoding insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

[0917] The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

[0918] Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D.^{600}$) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

[0919] Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl or preferably in 8 M urea and concentrations greater than 0.14 M 2-mercaptoethanol by stirring for 3-4 hours at 4°C (see, e.g., Burton et al., Eur. J. Biochem. *179*:379-387 (1989)). The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

[0920] Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8. The column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

[0921] The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. Exemplary conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

[0922] In addition to the above expression vector, the present invention further includes an expression vector, called pHE4a (ATCC Accession Number 209645, deposited on February 25, 1998) which contains phage operator and promoter elements operatively linked to a polynucleotide encoding an albumin fusion protein of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter and operator sequences are made synthetically.

[0923] DNA can be inserted into the pHE4a by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to PCR protocols described herein or otherwise known in the art, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

[0924] The engineered vector may be substituted in the above protocol to express protein in a bacterial system.

EXAMPLE 10: Isolation of a Selected cDNA Clone From the Deposited Sample.

[0925] Many of the albumin fusion constructs of the invention have been deposited with the ATCC as shown in Table 3. The albumin fusion constructs may comprise any one of the following expression vectors: the yeast *S. cerevisiae* expression vector pSAC35, the mammalian expression vector pC4, or the mammalian expression vector pEE12.1.

[0926] pSAC35 (Sleep *et al.*, 1990, Biotechnology 8:42), pC4 (ATCC Accession No. 209646; Cullen *et al.*, Molecular and Cellular Biology, 438-447 (1985); Boshart *et al.*, Cell 41: 521-530 (1985)), and pEE12.1 (Lonza Biologics, Inc.; Stephens and Cockett, Nucl. Acids Res. 17: 7110 (1989); International Publication #WO89/01036; Murphy *et al.*, Biochem J. 227: 277-279 (1991); Bebbington *et al.*, Bio/Technology 10:169-175

(1992); US patent US 5,122,464; International Publication #WO86/05807) vectors comprise an ampicillin resistance gene for growth in bacterial cells. These vectors and/or an albumin fusion construct comprising them can be transformed into an *E. coli* strain such as Stratagene XL-1 Blue (Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037) using techniques described in the art such as Hanahan, spread onto Luria-Broth agar plates containing 100 μg/mL ampicillin, and grown overnight at 37 °C.

[0927] The deposited material in the sample assigned the ATCC Deposit Number cited in Table 3 for any given albumin fusion construct also may contain one or more additional albumin fusion constructs, each encoding different albumin fusion proteins. Thus, deposits sharing the same ATCC Deposit Number contain at least an albumin fusion construct identified in the corresponding row of Table 3.

[0928] Two approaches can be used to isolate a particular albumin fusion construct from the deposited sample of plasmid DNAs cited for that albumin fusion construct in Table 3.

Method 1: Screening

[0929] First, an albumin fusion construct may be directly isolated by screening the sample of deposited plasmid DNAs using a polynucleotide probe corresponding to SEQ ID NO:X for an individual construct ID number in Table 1, using methods known in the art. For example, a specific polynucleotide with 30-40 nucleotides may be synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide can be labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982)). The albumin fusion construct from a given ATCC deposit is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Method 2: PCR

[0930] Alternatively, DNA encoding a given albumin fusion protein may be amplified from a sample of a deposited albumin fusion construct with SEQ ID NO:X, for example, by using two primers of 17-20 nucleotides that hybridize to the deposited albumin fusion construct 5' and 3' to the DNA encoding a given albumin fusion protein. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

[0931] Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res., 21(7):1683-1684 (1993)).

[0932] Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

[0933] This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

[0934] This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

EXAMPLE 11: Multifusion Fusions.

[0935] The albumin fusion proteins (e.g,. containing a Therapeutic protein (or fragment or variant thereof) fused to albumin (or a fragment or variant thereof)) may additionally be fused to other proteins to generate "multifusion proteins". These multifusion proteins can be used for a variety of applications. For example, fusion of the albumin fusion proteins of the invention to His-tag, HA-tag, protein A, IgG domains, and maltose

binding protein facilitates purification. (See e.g., EP A 394,827; Traunecker et al., Nature 331:84-86 (1988)). Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of an albumin fusion protein. Furthermore, the fusion of additional protein sequences to the albumin fusion proteins of the invention may further increase the solubility and/or stability of the fusion protein. The fusion proteins described above can be made using or routinely modifting techniques known in the art and/or by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule.

[0936] Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian or yeast expression vector.

[0937] For example, if pC4 (ATCC Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide encoding an albumin fusion protein of the present invention (generateed and isolated using techniques known in the art), is ligated into this BamHI site. Note that the polynucleotide encoding the fusion protein of the invention is cloned without a stop codon, otherwise a Fc containing fusion protein will not be produced.

[0938] If the naturally occurring signal sequence is used to produce the albumin fusion protein of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

[0939] Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCC
TCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGCCACGAAGACC
CTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG
TACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTC
CCAACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGA
GCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC
AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGA
GCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT
CTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:52)

EXAMPLE 12: Production of an Antibody from an Albumin Fusion Protein.

Hybridoma Technology

[0940] Antibodies that bind the albumin fusion proteins of the present invention and portions of the albumin fusion proteins of the present invention (e.g., the Therapeutic protein portion or albumin portion of the fusion protein) can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, a preparation of an albumin fusion protein of the invention or a portion of an albumin fusion protein of the invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

[0941] Monoclonal antibodies specific for an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention, are prepared using hybridoma technology (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention. The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention.

[0942] Alternatively, additional antibodies capable of binding to an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the an albumin fusion protein of the invention (or portion of an albumin fusion protein of the invention) -specific antibody can be blocked by the fusion protein of the invention, or a portion of an albumin fusion protein of the invention. Such antibodies comprise anti-idiotypic antibodies to the fusion protein of the invention (or portion of an albumin fusion protein of the invention) -specific antibody and are used to immunize an animal to induce formation

of further fusion protein of the invention (or portion of an albumin fusion protein of the invention) -specific antibodies.

[0943] For *in vivo* use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., International Publication No. WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985)).

[0944] *Isolation Of Antibody Fragments Directed Against an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention From A Library Of scFvs.* Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention, to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

[0945] *Rescue of the Library.* A library of scFvs is constructed from the RNA of human PBLs as described in International Publication No. WO 92/01047. To rescue phage displaying antibody fragments, approximately 10^9 *E. coli* harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 μg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see International Publication No. WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in International Publication No. WO 92/01047.

[0946] M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10^{13} transducing units/ml (ampicillin-resistant clones).

[0947] *Panning of the Library.* Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10^{13} TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

[0948] *Characterization of Binders.* Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention, in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., International Publication No. WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

EXAMPLE 13: [^{3}H]-2-Deoxyglucose Uptake Assay.

[0949] Adipose, skeletal muscle, and liver are insulin-sensitive tissues. Insulin can stimulate glucose uptake/transport into these tissues. In the case of adipose and skeletal muscle, insulin initiates the signal transduction that eventually leads to the translocation of the glucose transporter 4 molecule, GLUT4, from a specialized intracellular compartment to the cell surface. Once on the cell surface, GLUT4 allows for glucose uptake/transport.

[^{3}H]-2-Deoxyglucose Uptake

[0950] A number of adipose and muscle related cell-lines can be used to test for glucose uptake/transport activity in the absence or presence of a combination of any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus. In particular, the 3T3-L1 murine fibroblast cells and the L6 murine skeletal muscle cells can be differentiated into 3T3-L1 adipocytes and into myotubes, respectively, to serve as appropriate *in vitro* models for the [^{3}H]-2-deoxyglucose uptake assay (Urso et al., J Biol Chem, 274(43): 30864-73 (1999); Wang et al., J Mol Endocrinol, 19(3):

241-8 (1997); Haspel et al., J Membr Biol, 169 (1): 45-53 (1999); Tsakiridis et al., Endocrinology, 136(10): 4315-22 (1995)). Briefly, 2 x 10^5 cells/100 µL of adipocytes or differentiated L6 cells are transferred to 96-well Tissue-Culture, "TC", treated, i.e., coated with 50 µg/mL of poly-L-lysine, plates in post-differentiation medium and are incubated overnight at 37 °C in 5% CO_2. The cells are first washed once with serum free low glucose DMEM medium and are then starved with 100 µL/well of the same medium and with 100 µL/well of either buffer or of a combination of any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus, for example, increasing concentrations of 1 nM, 10 nM, and 100 nM of the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof) for 16 hours at 37 °C in the absence or presence of 1 nM insulin. The plates are washed three times with 100 µL/well of HEPES buffered saline. Insulin is added at 1 nM in HEPES buffered saline for 30 min at 37 °C in the presence of 10 µM labeled [^{3}H]-2-deoxyglucose (Amersham, #TRK672) and 10 µM unlabeled 2-deoxyglucose (SIGMA, D-3179). As control, the same conditions are carried out except in the absence of insulin. A final concentration of 10 µM cytochalasin B (SIGMA, C6762) is added at 100 µL/well in a separate well to measure the non-specific uptake. The cells are washed three times with HEPES buffered saline. Labeled, i.e., 10 µM of [^{3}H]-2-deoxyglucose, and unlabeled, i.e., 10 µM of 2-deoxyglucose, are added for 10 minutes at room temperature. The cells are washed three times with cold Phosphate Buffered *Sal* ine, "PBS". The cells are lysed upon the addition of 150 µL/well of 0.2 N NaOH and subsequent incubation with shaking for 20 minutes at room temperature. Samples are then transferred to a scintillation vial to which is added 5 mL of scintillation fluid. The vials are counted in a Beta-Scintillation counter. Uptake in duplicate conditions, the difference being the absence or presence of insulin, is determined with the following equation: [(Insulin counts per minute "cpm" – Non-Specific cpm)/(No Insulin cpm – Non-Specific cpm)]. Average responses fall within the limits of about 5-fold and 3-fold that of controls for adipocytes and myotubes, respectively.

Differentiation of Cells

[0951] The cells are allowed to become fully confluent in a T-75 cm² flask. The medium is removed and replaced with 25 mL of pre-differentiation medium for 48 hours. The cells are incubated at 37 °C, in 5% CO_2, 85% humidity. After 48 hours, the pre-differentiation medium is removed and replaced with 25 mL differentiation medium for 48 hours. The cells are again incubated at 37 °C, in 5% CO_2, 85% humidity. After 48 hours, the medium is removed and replaced with 30 mL post-differentiation medium. Post-differentiation medium is maintained for 14-20 days or until complete differentiation is achieved. The medium is changed every 2-3 days. Human adipocytes can be purchased from Zen-Bio, INC (# SA-1096).

EXAMPLE 14: In vitro Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines.

[0952] It has recently been shown that GLP-1 induces differentiation of the rat pancreatic ductal epithelial cell-line ARIP in a time- and dose-dependent manner which is associated with an increase in Islet Duodenal Homeobox-1 (IDX-1) and insulin mRNA levels (Hui et al., 2001, Diabetes, 50(4): 785-96). The IDX-1 in turn increases mRNA levels of the GLP-1 receptor.

Cells Types Tested

[0953] RIN-M cells: These cells are available from the American Type Tissue Culture Collection (ATCC Cell Line Number CRL-2057). The RIN-M cell line was derived from a radiation induced transplantable rat islet cell tumor. The line was established from a nude mouse xenograft of the tumor. The cells produce and secrete islet polypeptide hormones, and produce L-dopa decarboxylase (a marker for cells having amine precursor uptake and decarboxylation, or APUD, activity).

[0954] ARIP cells: These are pancreatic exocrine cells of epithelial morphology available from the American Type Tissue Culture Collection (ATCC Cell Line Number CRL-1674). See also, references: Jessop, N.W. and Hay, R.J., "Characteristics of two rat pancreatic exocrine cell lines derived from transplantable tumors," In Vitro 16: 212, (1980); Cockell, M. et al., "Identification of a cell-specific DNA-binding activity that interacts with a transcriptional activator of genes expressed in the acinar pancreas," Mol. Cell. Biol. 9: 2464-2476, (1989); Roux, E., et al. "The cell-specific transcription factor PTF1 contains two different subunits that interact with the DNA" Genes Dev. 3: 1613-1624, (1989); and, Hui, H., et al., "Glucagon-like peptide 1 induces differentiation of islet duodenal homeobox-1-positive pancreatic ductal cells into insulin-secreting cells," Diabetes 50: 785-796 (2001).

Preparation of Cells

[0955] The RIN-M cell-line is grown in RPMI 1640 medium (Hyclone, #SH300027.01) with 10% fetal bovine serum (HyClone, #SH30088.03) and is subcultured every 6 to 8 days at a ratio of 1:3 to 1:6. The medium is changed every 3 to 4 days.

[0956] The ARIP (ATCC #CRL-1674) cell-line is grown in Ham's F12K medium (ATCC, #30-2004) with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate and 10% fetal bovine serum. The ARIP cell-line is subcultured at a ratio of 1:3 to 1:6 twice per week. The medium is changed every 3 to 4 days.

Assay Protocol

[0957] The cells are seeded at 4000 cells/well in 96-well plates and cultured for 48 to 72 hours to 50% confluence. The cells are switched to serum-free media at 100 µL/well. After incubation for 48-72 hours, serum and/or the therapeutics of the subject invention (e.g., albumin fusion proteins of the invention and fragments and variants thereof) are added to the well. Incubation persists for an additional 36 hours. [^{3}H]-Thymidine

(5-20 Ci/mmol) (Amersham Pharmacia, #TRK120) is diluted to 1 microCuries/5 microliters. After the 36 hour incubation, 5 microliters is added per well for a further 24 hours. The reaction is terminated by washing the cells gently with cold Phosphate-Buffered *Sal* ine, "PBS", once. The cells are then fixed with 100 microliters of 10% ice cold TCA for 15 min at 4 °C. The PBS is removed and 200 microliters of 0.2 N NaOH is added. The plates are incubated for 1 hour at room temperature with shaking. The solution is transferred to a scintillation vial and 5 mL of scintillation fluid compatible with aqueous solutions is added and mixed vigorously. The vials are counted in a beta scintillation counter. As negative control, only buffer is used. As a positive control fetal calf serum is used.

EXAMPLE 15: Assaying for Glycosuria.

[0958] Glycosuria (i.e., excess sugar in the urine), can be readily assayed to provide an index of the disease state of diabetes mellitus. Excess urine in a patient sample as compared with a normal patient sample is symptomatic of IDDM and NIDDM. Efficacy of treatment of such a patient having IDDM and NIDDM is indicated by a resulting decrease in the amount of excess glucose in the urine. In a preferred embodiment for IDDM and NIDDM monitoring, urine samples from patients are assayed for the presence of glucose using techniques known in the art. Glycosuria in humans is defined by a urinary glucose concentration exceeding 100 mg per 100 ml. Excess sugar levels in those patients exhibiting glycosuria can be measured even more precisely by obtaining blood samples and assaying serum glucose.

EXAMPLE 16: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation.

[0959] Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

[0960] One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

[0961] In Vitro Assay- Albumin fusion proteins of the invention (including fusion proteins containing fragments or variants of Therapeutic proteins and/or albumin or fragments or variants of albumin) can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of an albumin fusion protein of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

[0962] Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5 X 10^{-5}M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

[0963] *In vivo* Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of an albumin fusion protein of the invention (including fusion proteins containing fragments or variants of Therapeutic proteins and/or albumin or fragments or variants of albumin). Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with the albumin fusion protein of the invention identify the results of the activity of the fusion protein on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

[0964] Flow cytometric analyses of the spleens from mice treated with the albumin fusion protein is used to indicate whether the albumin fusion protein specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

[0965] Likewise, a predicted consequence of increased mature B-cell representation *in vivo* is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and fusion protein treated mice.

EXAMPLE 17: T Cell Proliferation Assay.

[0966] A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ^{3}H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 μl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 μg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10^4/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of an albumin fusion protein of the invention (including fusion proteins containing fragments or variants of Therapeutic proteins and/or albumin or fragments or variants of albumin) (total volume 200 ul). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 μl of supernatant is removed and stored –20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 ul of medium containing 0.5 uCi of ^{3}H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of ^{3}H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative control for the effects of fusion proteins of the invention.

EXAMPLE 18: Effect of Fusion Proteins of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells.

[0967] Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF-α, causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FCγRII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

[0968] FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of an albumin fusion protein of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

[0969] Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Thl helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells (10^6/ml) are treated with increasing concentrations of an albumin fusion protein of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

[0970] Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increased expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

[0971] FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of an albumin fusion protein of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

[0972] Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Albumin fusion proteins of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

[0973] Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated processes (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the fusion protein to be tested. Cells are suspended at a concentration of 2 x 10^6/ml in PBS containing PI at a final concentration of 5 μg/ml, and then incubated at room temperature for 5 minutes before FACScan analysis. PI

uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

[0974] Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of $5x10^5$ cells/ml with increasing concentrations of an albumin fusion protein of the invention and under the same conditions, but in the absence of the fusion protein. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in the presence of the fusion protein. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g., R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

[0975] Oxidative burst. Purified monocytes are plated in 96-w plate at $2\text{-}1x10^5$ cell/well. Increasing concentrations of an albumin fusion protein of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H_2O_2 produced by the macrophages, a standard curve of a H_2O_2 solution of known molarity is performed for each experiment.

EXAMPLE 19: The Effect of Albumin Fusion Proteins of the Invention on the Growth of Vascular Endothelial Cells.

[0976] On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at $2\text{-}5x10^4$ cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnique, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An albumin fusion protein of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

[0977] An increase in the number of HUVEC cells indicates that the fusion protein may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cells indicates that the fusion protein inhibits vascular endothelial cells.

EXAMPLE 20: Rat Corneal Wound Healing Model.

[0978] This animal model shows the effect of an albumin fusion protein of the invention on neovascularization. The experimental protocol includes:

Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

Inserting a spatula below the lip of the incision facing the outer corner of the eye.

Making a pocket (its base is 1-1.5 mm form the edge of the eye).

Positioning a pellet, containing 50ng- 5ug of an albumin fusion protein of the invention, within the pocket.

Treatment with an an albumin fusion protein of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

EXAMPLE 21: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models.

Diabetic db+/db+ Mouse Model.

[0979] To demonstrate that an albumin fusion protein of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al., J. Surg. Res. 52*:389 (1992); Greenhalgh, D.G. *et.al., Am. J. Pathol. 136*:1235 (1990)).

[0980] The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al. Proc. Natl. Acad. Sci. USA 77*:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al., J. Immunol. 120*:1375 (1978); Debray-Sachs, M. *et al., Clin. Exp. Immunol. 51(1)*:1-7 (1983); Leiter *et al., Am. J. of Pathol. 114*:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al., Exp. Neurol. 83(2)*:221-232 (1984); Robertson *et al., Diabetes 29(1)*:60-67 (1980); Giacomelli *et al., Lab Invest. 40(4)*:460-473 (1979); Coleman, D.L., *Diabetes 31 (Suppl)*:1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al., J. Immunol. 120*:1375-1377 (1978)).

[0981] The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al., Am. J. of Pathol. 136*:1235-1246 (1990)).

[0982] Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually

housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

[0983] Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med. 172*:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

[0984] Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

[0985] An albumin fusion protein of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

[0986] Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

[0987] Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

[0988] Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm^2, the corresponding size of the dermal punch. Calculations are made using the following formula:

a. [Open area on day 8] - [Open area on day 1] / [Open area on day 1]

[0989] Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an albumin fusion protein of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al., Am. J. Pathol. 136*:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

[0990] Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

[0991] Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

[0992] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

Steroid Impaired Rat Model

[0993] The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl*et al., J. Immunol. 115*: 476-481 (1975); Werb *et al., J. Exp. Med. 147*:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al., An. Intern. Med. 37*:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes et al., *J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In:* Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In*: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al., Proc. Natl. Acad. Sci. USA 86*: 2229-2233 (1989)).

[0994] To demonstrate that an albumin fusion protein of the invention can accelerate the healing process, the effects of multiple topical

applications of the fusion protein on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

[0995] Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

[0996] The wounding protocol is followed according to that described above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

[0997] Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

[0998] The fusion protein of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

[0999] Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

[1000] Three groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

[1001] Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is $64mm^2$, the corresponding size of the dermal punch. Calculations are made using the following formula:

b. [Open area on day 8] - [Open area on day 1] / [Open area on day 1]

[1002] Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an albumin fusion protein of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

[1003] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

EXAMPLE 22: Lymphedema Animal Model

[1004] The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an albumin fusion protein of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

[1005] Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

[1006] Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

[1007] Using a microscope, muscles in back of the leg (near the semitendinosis and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

[1008] Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by

using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

[1009] To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect of plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

[1010] Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people and those 2 readings are averaged. Readings are taken from both control and edematous limbs.

[1011] Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), and both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

[1012] Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and $Ca2^+$ comparison.

[1013] Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

[1014] Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

EXAMPLE 23: Suppression of TNF alpha-Induced Adhesion Molecule Expression by an Albumin Fusion Protein of the Invention.

[1015] The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

[1016] Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

[1017] The potential of an albumin fusion protein of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

[1018] To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO_2. HUVECs are seeded in 96-well plates at concentrations of 1×10^4 cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

[1019] Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μl of 0.1% paraformaldehyde-PBS(with Ca^{++} and Mg^{++}) is added to each well. Plates are held at 4°C for 30 min.

[1020] Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 μl of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified

environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

[1021] Then add 20 μl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 μl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μl of pNNP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 μl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

EXAMPLE 24: Construction of GAS Reporter Construct.

[1022] One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

[1023] GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

[1024] The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

[1025] The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995)). A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xaa-Trp-Ser (SEQ ID NO:53)).

[1026] Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway (See Table 5, below). Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

Table 5

JAKs Ligand	tyk2	STATS Jak1	Jak2	Jak3	GAS(elements) or ISRE	
IFN family						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10	+	?	?	-	1,3	
gp130 family						
IL-6 (Pleiotropic)	+	+	+	?	1,3	GAS(IRF1>Lys6>IFP)
Il-11(Pleiotropic)	?	+	?	?	1,3	
OnM(Pleiotropic)	?	+	+	?	1,3	
LIF(Pleiotropic)	?	+	+	?	1,3	
CNTF(Pleiotropic)	-/+	+	+	?	1,3	
G-CSF(Pleiotropic)	?	+	?	?	1,3	
IL-12(Pleiotropic)	+	-	+	+	1,3	
g-C family						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS(IRF1=IFP>>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
gp140 family						

IL-3 (myeloid)	-	-	+	-	5	GAS(IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
Growth hormone family						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS (B-CAS>IRF1=IFP>>Ly6)
Receptor Tyrosine Kinases						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS(not IRF1)

[1027] To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 27-29, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:54)

[1028] The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:55)

[1029] PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:56)

[1030] With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

[1031] The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

[1032] Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 27-29.

[1033] Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing EGR and NF-KB promoter sequences are described in Examples 27-31. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

EXAMPLE 25: Assay for SEAP Activity.

[1034] As a reporter molecule for the assays described in examples disclosed herein, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

[1035] Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a solution containing an albumin fusion protein of the invention. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

[1036] Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer

and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the Table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on a luminometer, thus one should treat 5 plates at each time and start the second set 10 minutes later.

[1037] Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Table 6

# of plates	Rxn buffer diluent (ml)	CSPD (ml)	# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3	31	165	8.25
11	65	3.25	32	170	8.5
12	70	3.5	33	175	8.75
13	75	3.75	34	180	9
14	80	4	35	185	9.25
15	85	4.25	36	190	9.5
16	90	4.5	37	195	9.75
17	95	4.75	38	200	10
18	100	5	39	205	10.25
19	105	5.25	40	210	10.5
20	110	5.5	41	215	10.75
21	115	5.75	42	220	11
22	120	6	43	225	11.25
23	125	6.25	44	230	11.5
24	130	6.5	45	235	11.75
25	135	6.75	46	240	12
26	140	7	47	245	12.25
27	145	7.25	48	250	12.5
28	150	7.5	49	255	12.75
29	155	7.75	50	260	13
30	160	8			

EXAMPLE 26: Assay Identifying Neuronal Activity.

[1038] When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, the ability of fusion proteins of the invention to activate cells can be assessed.

[1039] Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by an albumin fusion protein of the present invention can be assessed.

[1040] The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

First primer: 5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG-3' (SEQ ID NO:57)

Second primer: 5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:58)

[1041] Using the GAS:SEAP/Neo vector produced in Example 24, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

[1042] To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

[1043] PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

[1044] Transfect the EGR/SEAP/Neo construct into PC12 using techniques known in the art. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

[1045] To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the

cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

[1046] The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

[1047] Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to $1x10^5$ cells/well). Add a series of different concentrations of an albumin fusion protein of the inventon, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay may be routinely performed using techniques known in the art and/or as described in Example 25.

EXAMPLE 27: Assay for T-cell Activity.

[1048] The following protocol is used to assess T-cell activity by identifying factors, and determining whether an albumin fusion protein of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 24. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

[1049] Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

[1050] Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

[1051] During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1 x 10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

[1052] The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with varying concentrations of one or more fusion proteins of the present invention.

[1053] On the day of treatment with the fusion protein, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of fusion proteins and the number of different concentrations of fusion proteins being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

[1054] The well dishes containing Jurkat cells treated with the fusion protein are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 25. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

[1055] As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

[1056] The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

EXAMPLE 28: Assay for T-cell Activity.

[1057] NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

[1058] In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

[1059] Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the fusion protein. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

[1060] To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four

tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:59), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:60)

[1061] The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:55)

[1062] PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGC CCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAG GCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:61)

[1063] Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

[1064] In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

[1065] Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 25. Similarly, the method for assaying fusion proteins with these stable Jurkat T-cells is also described in Example 25. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

EXAMPLE 29: Assay Identifying Myeloid Activity.

[1066] The following protocol is used to assess myeloid activity of an albumin fusion protein of the present invention by determining whether the fusion protein proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 24. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

[1067] To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 24, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest $2x10^7$ U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

[1068] Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $Na_2HPO_4.7H_2O$, 1 mM $MgCl_2$, and 675 uM $CaCl_2$. Incubate at 37 degrees C for 45 min.

[1069] Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

[1070] The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

[1071] These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

[1072] Add different concentrations of the fusion protein. Incubate at 37 degee C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to methods known in the art and/or the protocol described in Example 25.

EXAMPLE 30: Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability.

[1073] Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify fusion proteins which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

[1074] The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

[1075] For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in

a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

[1076] A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

[1077] For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

[1078] For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The fusion protein of the invention is added to the well, and a change in fluorescence is detected.

[1079] To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by an albumin fusion protein of the present invention or a molecule induced by an albumin fusion protein of the present invention, which has resulted in an increase in the intracellular Ca^{++} concentration.

EXAMPLE 31: Assay Identifying Tyrosine Kinase Activity.

[1080] The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

[1081] Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

[1082] Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether an albumin fusion protein of the present invention or a molecule induced by a fusion proetin of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

[1083] Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

[1084] To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or a different concentrations of an albumin fusion protein of the invention, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN)) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4^{0}C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

[1085] Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

[1086] Generally, the tyrosine kinase activity of an albumin fusion protein of the invention is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include

PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

[1087] The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg_{2+} (5mM ATP/50mM $MgCl_2$), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

[1088] The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

[1089] Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

[1090] Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

EXAMPLE 32: Assay Identifying Phosphorylation Activity.

[1091] As a potential alternative and/or complement to the assay of protein tyrosine kinase activity described in Example 31, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

[1092] Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

[1093] A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or varying concentrations of the fusion protein of the invention for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

[1094] After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by the fusion protein of the present invention or a molecule induced by an albumin fusion protein of the present invention.

EXAMPLE 33: Phosphorylation Assay.

[1095] In order to assay for phosphorylation activity of an albumin fusion protein of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a protein substrate using gamma-labeled ^{32}P-ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The fusion portein of the invention is incubated with the protein substrate, ^{32}P-ATP, and a kinase buffer. The ^{32}P incorporated into the substrate is then separated from free ^{32}P-ATP by electrophoresis, and the incorporated ^{32}P is counted and compared to a negative control. Radioactivity counts above the negative control are indicative of phosphorylation activity of the fusion protein.

EXAMPLE 34: Detection of Phosphorylation Activity (Activation) of an Albumin Fusion Protein of the Invention in the Presence of Polypeptide Ligands.

[1096] Methods known in the art or described herein may be used to determine the phosphorylation activity of an albumin fusion protein of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in US 5,817,471 (incorporated herein by reference).

EXAMPLE 35: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation.

[1097] This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the

ability of fusion proteins of the inventon to stimulate proliferation of CD34+ cells.

[1098] It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of fusion proteins of the invention on hematopoietic activity of a wide range of progenitor cells, the assay contains a given fusion protein of the invention in the presence or absence of hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested fusion protein has a stimulatory effect on hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given fusion protein might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

[1099] Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5 x 10^5 cells/ml. During this time, 100 μl of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with an albumin fusion protein of the invention in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 μl of prepared cytokines, varying concentrations of an albumin fusion protein of the invention, and 20 μl of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100 μl. The plates are then placed in a 37°C/5% CO_2 incubator for five days.

[1100] Eighteen hours before the assay is harvested, 0.5 μCi/well of [3H] Thymidine is added in a 10 μl volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 μl Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film A bar code 15 sticker is affixed to the first plate for counting. The sealed plates are then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

[1101] The studies described in this example test the activity of a given fusion protein to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of fusion porteins and polynucleotides of the invention (e.g., gene therapy) as well as agonists and antagonists thereof. The ability of an albumin fusion protein of the invention to stimulate the proliferation of bone marrow CD34+ cells indicates that the albumin fusion protein and/or polynucleotides corresponding to the fusion protein are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

EXAMPLE 36: Assay for Extracellular Matrix Enhanced Cell Response (EMECR).

[1102] The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to evaluate the ability of fusion proteins of the invention to act on hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

[1103] Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5.\beta_1$ and $\alpha_4.\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and are responsible for stimulating stem cell self-renewal havea not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

[1104] Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of 0.2 μg/ cm^2. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Albumin fusion proteins of the invention are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where volume of the administed composition containing the albumin fusion protein of the invention represents 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO_2, 7% O_2, and 88% N_2) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

[1105] If a particular fusion protein of the present invention is found to be a stimulator of hematopoietic progenitors, the fusion protein and polynucleotides corresponding to the fusion protein may be useful for example, in the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The fusion protein may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

[1106] Additionally, the albumin fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

[1107] Moreover, fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

EXAMPLE 37: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation.

[1108] An albumin fusion protein of the invention is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the fusion protein on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNFa stimulation, in order to check for costimulatory or inhibitory activity.

[1109] Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 µl culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 µg/ml hEGF, 5mg/ml insulin, 1µg/ml hFGF, 50mg/ml gentamycin, 50 µg/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50µg/ml Amphotericin B, 0.4% FBS. Incubate at 37 °C until day 2.

[1110] On day 2, serial dilutions and templates of an albumin fusion protein of the invention are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or an albumin fusion protein of the invention and incubate at 37 degrees C/5% CO_2 until day 5.

[1111] Transfer 60µl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4 degrees C until Day 6 (for IL6 ELISA). To the remaining 100 µl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10µl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

[1112] On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 ul/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

[1113] On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 µl/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 µl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

[1114] Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels.

[1115] Add 100 µl/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay were tabulated and averaged.

[1116] A positive result in this assay suggests AoSMC cell proliferation and that the albumin fusion protein may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of the fusion protein and polynucleotides encoding the albumin fusion protein. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, fusion proteins may be used in wound healing and dermal regeneration, as well as the promotion of vasculogenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular

diseases. Additionally, fusion proteins showing antagonistic activity in this assay may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular agent (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, albumin fusion proteins that act as antagonists in this assay may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

EXAMPLE 38: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells.

[1117] The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

[1118] Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μl of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing (containing an albumin fusion protein of the invention) and positive or negative controls are added to the plate in triplicate (in 10 μl volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 μl of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μl of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 μl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μl of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 μl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

EXAMPLE 39: Alamar Blue Endothelial Cells Proliferation Assay.

[1119] This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

[1120] Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37 degreesC overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of an albumin fusion protein of the invention or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

[1121] Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth

medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form (i.e., stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity). The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

EXAMPLE 40: Detection of Inhibition of a Mixed Lymphocyte Reaction.

[1122] This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by fusion proteins of the invention. Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by the albumin fusion proteins that inhibit MLR since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

[1123] Albumin fusion proteins of the invention found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

[1124] Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM®, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2×10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2×10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of the fusion protein test material (50 μl) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μg/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 μg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO_2, and 1 μC of [^{3}H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

[1125] Samples of the fusion protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

EXAMPLE 41: Assays for Protease Activity.

[1126] The following assay may be used to assess protease activity of an albumin fusion protein of the invention.

[1127] Gelatin and casein zymography are performed essentially as described (Heusen et al., *Anal. Biochem.*, 102:196-202 (1980); Wilson et al., *Journal of Urology*, 149:653-658 (1993)). Samples are run on 10% polyacryamide/0.1% SDS gels containing 1% gelain orcasein, soaked in 2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours. After staining in amido black areas of proteolysis apear as clear areas agains the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

[1128] Protease activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mMNaPO$_4$,1mM EDTA, and 1mM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260nm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive control.

[1129] Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., *Methods of Enzymatic Analysis*, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward, *Applied Science*, 251-317 (1983)).

EXAMPLE 42: Identifying Serine Protease Substrate Specificity.

[1130] Methods known in the art or described herein may be used to determine the substrate specificity of the albumin fusion proteins of the present invention having serine protease activity. A preferred method of determining substrate specificity is by the use of positional scanning synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its entirety).

EXAMPLE 43: Ligand Binding Assays.

[1131] The following assay may be used to assess ligand binding activity of an albumin fusion protein of the invention.

[1132] Ligand binding assays provide a direct method for ascertaining receptor pharmacology and are adaptable to a high throughput format. The purified ligand for an albumin fusion protein of the invention is radiolabeled to high specific activity (50-2000 Ci/mmol) for binding studies. A determination is then made that the process of radiolabeling does not diminish the activity of the ligand towards the fusion protein. Assay conditions for buffers, ions, pH and other modulators such as nucleotides are optimized to establish a workable signal to noise ratio for both membrane and whole cell polypeptide sources. For these assays, specific polypeptide binding is defined as total associated radioactivity minus the radioactivity

measured in the presence of an excess of unlabeled competing ligand. Where possible, more than one competing ligand is used to define residual nonspecific binding.

EXAMPLE 44: Functional Assay in Xenopus Oocytes.

[1133] Capped RNA transcripts from linearized plasmid templates encoding an albumin fusion protein of the invention is synthesized in vitro with RNA polymerases in accordance with standard procedures. In vitro transcripts are suspended in water at a final concentration of 0.2 mg/mi. Ovarian lobes are removed from adult female toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocytc) are injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage clamps are used to measure the currents from individual *Xenopus oocytes* in response fusion protein and polypeptide agonist exposure. Recordings are made in Ca2+ free Barth's medium at room temperature. The Xenopus system can be used to screen known ligands and tissue/cell extracts for activating ligands.

EXAMPLE 45: Microphysiometric Assays.

[1134] Activation of a wide variety of secondary messenger systems results in extrusion of small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the ability of an albumin fusion protein of the invention to activate secondary messengers that are coupled to an energy utilizing intracellular signaling pathway.

EXAMPLE 46: Extract/Cell Supernatant Screening.

[1135] A large number of mammalian receptors exist for which there remains, as yet, no cognate activating ligand (agonist). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the albumin fusion proteins of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify natural ligands for the Therapeutic protein portion and/or albumin protein portion of an albumin fusion protein of the invention. Extracts that produce positive functional responses can be sequentially subfractionated until an activating ligand is isolated and identified.

EXAMPLE 47: ATP-binding assay.

[1136] The following assay may be used to assess ATP-binding activity of fusion proteins of the invention.

[1137] ATP-binding activity of an albumin fusion protein of the invention may be detected using the ATP-binding assay described in U.S. Patent 5,858,719, which is herein incorporated by reference in its entirety. Briefly, ATP-binding to an albumin fusion protein of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of ABC transport protein are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenyl-5'-imidodiphosphate for 10 minutes at 4°C. A mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP (^{32}P-ATP) (5 mCi/μmol, ICN, Irvine CA.) is added to a final concentration of 100 μM and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 nm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition of dithiothreitol to a final concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the albumin fusion proteins of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing ATP or adenly-5'-imidodiphosphate provides a measure of ATP affinity to the fusion protein.

EXAMPLE 48: Identification Of Signal Transduction Proteins That Interact With An albumin fusion protein Of The Present Invention.

[1138] Albumin fusion proteins of the invention may serve as research tools for the identification, characterization and purification of signal transduction pathway proteins or receptor proteins. Briefly, a labeled fusion protein of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, an albumin fusion protein of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the albumin fusion protein. The protein complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

EXAMPLE 49: IL-6 Bioassay.

[1139] A variety of assays are known in the art for testing the proliferative effects of an albumin fusion protein of the invention. For example, one such asssay is the IL-6 Bioassay as described by Marz *et al.* (*Proc. Natl. Acad. Sci., U.S.A.*, *95*:3251-56 (1998), which is herein incorporated by reference). After 68 hrs. at 37°C, the number of viable cells is measured by adding the tetrazolium salt thiazolyl blue (MTT) and incubating for a further 4 hrs. at 37°C. B9 cells are lysed by SDS and optical density is measured at 570 nm. Controls containing IL-6 (positive) and no cytokine (negative) are Briefly, IL-6 dependent B9 murine cells are washed three times in IL-6 free medium and plated at a concentration of 5,000 cells per well in 50 μl, and 50 μl of fusion protein of the invention is added. utilized. Enhanced proliferation in the test sample(s) (containing an albumin fusion protein of the invention) relative to the negative control is indicative of proliferative effects mediated by the fusion protein.

EXAMPLE 50: Support of Chicken Embryo Neuron Survival.

[1140] To test whether sympathetic neuronal cell viability is supported by an albumin fusion protein of the invention, the chicken embryo neuronal survival assay of Senaldi *et al* may be utilized (*Proc. Natl. Acad. Sci., U.S.A., 96*:11458-63 (1998), which is herein incorporated by reference). Briefly, motor and sympathetic neurons are isolated from chicken embryos, resuspended in L15 medium (with 10% FCS, glucose, sodium selenite, progesterone, conalbumin, putrescine, and insulin; Life Technologies, Rockville, MD.) and Dulbecco's modified Eagles medium [with 10% FCS, glutamine, penicillin, and 25 mM Hepes buffer (pH 7.2); Life Technologies, Rockville, MD.], respectively, and incubated at 37°C in 5% CO_2 in the presence of different concentrations of the purified fusion protein of the invention, as well as a negative control lacking any cytokine. After 3 days, neuron survival is determined by evaluation of cellular morphology, and through the use of the colorimetric assay of Mosmann (Mosmann, T., *J. Immunol. Methods, 65*:55-63 (1983)). Enhanced neuronal cell viability as compared to the controls lacking cytokine is indicative of the ability of the albumin fusion protein to enhance the survival of neuronal cells.

EXAMPLE 51: Assay for Phosphatase Activity.

[1141] The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of an albumin fusion protein of the invention.

[1142] In order to assay for serine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the serine/threonine phosphatase (PSPase) activity of an albumin fusion protein of the invention may be measured using a PSPase assay kit from New England Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on serine and threonine residues with cAMP-dependent Protein Kinase in the presence of [^{32}P]ATP. Protein serine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphate from 32P-labeled MyBP.

EXAMPLE 52: Interaction of Serine/Threonine Phosphatases with other Proteins.

[1143] Fusion proteins of the invention having serine/threonine phosphatase activity (e.g., as determined in Example 51) are useful, for example, as research tools for the identification, characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, a labeled fusion protein of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, an albumin fusion protein of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the fusion protein. The fusion protein -complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

EXAMPLE 53: Assaying for Heparanase Activity.

[1144] There a numerous assays known in the art that may be employed to assay for heparanase activity of an albumin fusion protein of the invention. In one example, heparanase activity of an albumin fusion protein of the invention, is assayed as described by Vlodavsky et al., (Vlodavsky et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media, intact cells (1 x 10^6 cells per 35-mm dish), cell culture supernatant, or purified fusion protein are incubated for 18 hrs at 37°C, pH 6.2-6.6, with ^{35}S-labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are eluted from Sepharose 6B at $0.5 < K_{av} < 0.8$ (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of an albumin fusion protein of the invention in cleaving heparan sulfate.

EXAMPLE 54: Immobilization of biomolecules.

[1145] This example provides a method for the stabilization of an albumin fusion protein of the invention in non-host cell lipid bilayer constucts (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999), hereby incorporated by reference in its entirety herein) which can be adapted for the study of fusion proteins of the invention in the various functional assays described above. Briefly, carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to an albumin fusion protein of the invention, thus allowing uniform orientation upon immobilization. A 50uM solution of an albumin fusion protein of the invention in washed membranes is incubated with 20 mM NaIO4 and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed (Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h, exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl, 1 mM MgCl2, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylglucoside).

EXAMPLE 55: Assays for Metalloproteinase Activity.

[1146] Metalloproteinases are peptide hydrolases which use metal ions, such as Zn^{2+}, as the catalytic mechanism. Metalloproteinase activity of an albumin fusion protein of the present invention can be assayed according to methods known in the art. The following exemplary methods are provided:

Proteolysis of alpha-2-macroglobulin

[1147] To confirm protease activity, a purified fusion protein of the invention is mixed with the substrate alpha-2-macroglobulin (0.2 unit/ml;

Boehringer Mannheim, Germany) in 1x assay buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, 25 μM $ZnCl_2$ and 0.05% Brij-35) and incubated at 37°C for 1-5 days. Trypsin is used as positive control. Negative controls contain only alpha-2-macroglobulin in assay buffer. The samples are collected and boiled in SDS-PAGE sample buffer containing 5% 2-mercaptoethanol for 5-min, then loaded onto 8% SDS-polyacrylamide gel. After electrophoresis the proteins are visualized by silver staining. Proteolysis is evident by the appearance of lower molecular weight bands as compared to the negative control.

Inhibition of alpha-2-macroglobulin proteolysis by inhibitors of metalloproteinases

[1148] Known metalloproteinase inhibitors (metal chelators (EDTA, EGTA, AND $HgCl_2$), peptide metalloproteinase inhibitors (TIMP-1 and TIMP-2), and commercial small molecule MMP inhibitors) may also be used to characterize the proteolytic activity of an albumin fusion protein of the invention. Three synthetic MMP inhibitors that may be used are: MMP inhibitor I, [IC_{50} = 1.0 μM against MMP-1 and MMP-8; IC_{50} = 30 μM against MMP-9; IC_{50} = 150 μM against MMP-3]; MMP-3 (stromelysin-1) inhibitor I [IC_{50} = 5 μM against MMP-3], and MMP-3 inhibitor II [K_i = 130 nM against MMP-3]; inhibitors available through Calbiochem, catalog # 444250, 444218, and 444225, respectively). Briefly, different concentrations of the small molecule MMP inhibitors are mixed with a purified fusion protein of the invention (50μg/ml) in 22.9 μl of 1x HEPES buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, 25 μM $ZnCl_2$ and 0.05%Brij-35) and incubated at room temperature (24 °C) for 2-hr, then 7.1 μl of substrate alpha-2-macroglobulin (0.2 unit/ml) is added and incubated at 37°C for 20-hr. The reactions are stopped by adding 4x sample buffer and boiled immediately for 5 minutes. After SDS-PAGE, the protein bands are visualized by silver stain.

Synthetic Fluorogenic Peptide Substrates Cleavage Assay

[1149] The substrate specificity for fusion proteins of the invention with demonstrated metalloproteinase activity may be determined using techniques knonw in the art, such as using synthetic fluorogenic peptide substrates (purchased from BACHEM Bioscience Inc). Test substrates include, M-1985, M-2225, M-2105, M-2110, and M-2255. The first four are MMP substrates and the last one is a substrate of tumor necrosis factor-α (TNF-α) converting enzyme (TACE). These substrastes are preferably prepared in 1:1 dimethyl sulfoxide (DMSO) and water. The stock solutions are 50-500 μM. Fluorescent assays are performed by using a Perkin Elmer LS 50B luminescence spectrometer equipped with a constant temperature water bath. The excitation λ is 328 nm and the emission λ is 393 nm. Briefly, the assay is carried out by incubating 176 μl 1x HEPES buffer (0.2 M NaCl, 10 mM $CaCl_2$, 0.05% Brij-35 and 50 mM HEPES, pH 7.5) with 4 μl of substrate solution (50 μM) at 25 °C for 15 minutes, and then adding 20 μl of a purified fusion protein of the invention into the assay cuvett. The final concentration of substrate is 1 μM. Initial hydrolysis rates are monitored for 30-min.

EXAMPLE 56: Occurrence of Diabetes in NOD Mice.

[1150] Female NOD (non-obese diabetic) mice are characterized by displaying IDDM with a course which is similar to that found in humans, although the disease is more pronounced in female than male NOD mice. Hereinafter, unless otherwise stated, the term "NOD mouse" refers to a female NOD mouse. NOD mice have a progressive destruction of beta cells which is caused by a chronic autoimmune disease. Thus, NOD mice begin life with euglycemia, or normal blood glucose levels. By about 15 to 16 weeks of age, however, NOD mice start becoming hyperglycemic, indicating the destruction of the majority of their pancreatic beta cells and the corresponding inability of the pancreas to produce sufficient insulin. Thus, both the cause and the progression of the disease are similar to human IDDM patients.

[1151] *In vivo* assays of efficacy of the immunization regimens can be assessed in female NOD/LtJ mice (commercially available from The Jackson Laboratory, Bar Harbor, Me.). In the literature, it's reported that 80% of female mice develop diabetes by 24 weeks of age and onset of insulitis begins between 6-8 weeks age. NOD mice are inbred and highly responsive to a variety of immunoregulatory strategies. Adult NOD mice (6-8 weeks of age) have an average mass of 20-25 g.

[1152] These mice can be either untreated (control), treated with the therapeutics of the subject invention (e.g., albumin fusion proteins of the invention and fragments and variants thereof), alone or in combination with other therapeutic compounds stated above. The effect of these various treatments on the progression of diabetes can be measured as follows:

[1153] At 14 weeks of age, the female NOD mice can be phenotyped according to glucose tolerance. Glucose tolerance can be measured with the intraperitoneal glucose tolerance test (IPGTT). Briefly, blood is drawn from the paraorbital plexus at 0 minutes and 60 minutes after the intraperitoneal injection of glucose (1 g/kg body weight). Normal tolerance is defined as plasma glucose at 0 minutes of less than 144 mg %, or at 60 minutes of less than 160 mg %. Blood glucose levels are determined with a Glucometer Elite apparatus.

[1154] Based upon this phenotypic analysis, animals can be allocated to the different experimental groups. In particular, animals with more elevated blood glucose levels can be assigned to the impaired glucose tolerance group. The mice can be fed ad libitum and can be supplied with acidified water (pH 2.3).

[1155] The glucose tolerant and intolerant mice can be further subdivided into control, albumin fusion proteins of the subject invention, and albumin fusion proteins/therapeutic compounds combination groups. Mice in the control group can receive an interperitoneal injection of vehicle daily, six times per week. Mice in the albumin fusion group can receive an interperitoneal injection of the therapeutics of the subject invention (e.g., albumin fusion proteins of the invention and fragments and variants thereof) in vehicle daily, six times per week. Mice in the albumin fusion

proteins/therapeutic compounds combination group can receive both albumin fusion proteins and combinations of therapeutic compounds as described above.

[1156] The level of urine glucose in the NOD mice can be determined on a bi-weekly basis using Labstix (Bayer Diagnostics, Hampshire, England). Weight and fluid intake can also be determined on a bi-weekly basis. The onset of diabetes is defined after the appearance of glucosuria on two consecutive determinations. After 10 weeks of treatment, an additional IPGTT can be performed and animals can be sacrificed the following day.

[1157] Over the 10 week course of treatment, control animals in both the glucose tolerant and glucose intolerant groups develop diabetes at a rate of 60% and 86%, respectively (see US patent No. 5,866,546, Gross et al.). Thus, high rates of diabetes occur even in NOD mice which are initially glucose tolerant if no intervention is made.

[1158] Results can be confirmed by the measurement of blood glucose levels in NOD mice, before and after treatment. Blood glucose levels are measured as described above in both glucose tolerant and intolerant mice in all groups described.

[1159] In an alternative embodiment, the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof) can be quantified using spectrometric analysis and appropriate protein quantities can be resuspended prior to injection in 50 .mu.l phosphate buffered saline (PBS) per dose. Two injections, one week apart, can be administered subcutaneously under the dorsal skin of each mouse. Monitoring can be performed on two separate occasions prior to immunization and can be performed weekly throughout the treatment and continued thereafter. Urine can be tested for glucose every week (Keto-Diastix.RTM.; Miles Inc., Kankakee, Ill.) and glycosuric mice can be checked for serum glucose (ExacTech.RTM., MediSense, Inc., Waltham, Mass.). Diabetes is diagnosed when fasting glycemia is greater than 2.5g/L.

EXAMPLE 57: Histological Examination of NOD Mice.

[1160] Histological examination of tissue samples from NOD mice can demonstrate the ability of the compositions of the present invention, and/or a combination of the compositions of the present invention with other therapeutic agents for diabetes, to increase the relative concentration of beta cells in the pancreas. The experimental method is as follows:

[1161] The mice from Example 56 can be sacrificed at the end of the treatment period and tissue samples can be taken from the pancreas. The samples can be fixed in 10% formalin in 0.9% saline and embedded in wax. Two sets of 5 serial 5 .mu.m sections can be cut for immunolabelling at a cutting interval of 150 .mu.m. Sections can be immunolabelled for insulin (guinea pig anti-insulin antisera dilution 1:1000, ICN Thames U.K.) and glucagon (rabbit anti-pancreatic glucagon antisera dilution 1:2000) and detected with peroxidase conjugated anti-guinea pig (Dako, High Wycombe, U.K.) or peroxidase conjugated anti-rabbit antisera (dilution 1:50, Dako).

[1162] The composition of the present invention may or may not have as strong an effect on the visible mass of beta cells as it does on the clinical manifestations of diabetes in glucose tolerant and glucose intolerant animals.

EXAMPLE 58: In vivo Mouse Model of NIDDM.

[1163] Male C57BL/6J mice from Jackson Laboratory (Bar Harbor, ME) can be obtained at 3 weeks of age and fed on conventional chow or diets enriched in either fat (35.5% wt/wt; Bioserv.Frenchtown, NJ) or fructose (60% wt/wt; Harlan Teklad, Madison, WI). The regular chow is composed of 4.5% wt/wt fat, 23% wt/wt protein, 31.9% wt/wt starch, 3.7% wt/wt fructose, and 5.3% wt/wt fiber. The high-fat (lard) diet is composed of 35.5% wt/wt fat, 20% wt/wt protein, 36.4% wt/wt starch, 0.0% wt/wt fructose, and 0.1% wt/wt fiber. The high-fructose diet is composed of 5% wt/wt fat, 20% wt/wt protein, 0.0% wt/wt starch, 60% wt/wt fructose, and 9.4% wt/wt fiber. The mice may be housed no more than five per cage at 22° +/- 3°C temperature- and 50% +/- 20% humidity-controlled room with a 12-hour light (6 am to 6 pm)/dark cycle (Luo et al., 1998, Metabolism 47(6): 663-8, "Nongenetic mouse models of non-insulin-dependent diabetes mellitus"; Larsen et al., Diabetes 50(11): 2530-9 (2001), "Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats"). After exposure to the respective diets for 3 weeks, mice can be injected intraperitoneally with either streptozotocin, "STZ" (Sigma, St. Louis, MO), at 100 mg/kg body weight or vehicle (0.05 mol/L citric acid, pH 4.5) and kept on the same diet for the next 4 weeks. Under nonfasting conditions, blood is obtained 1, 2, and 4 weeks post-STZ by nipping the distal part of the tail. Samples are used to measure nonfasting plasma glucose and insulin concentrations. Body weight and food intake are recorded weekly.

[1164] To directly determine the effect of the high-fat diet on the ability of insulin to stimulate glucose disposal, the experiments can be initiated on three groups of mice, fat-fed, chow-fed injected with vehicle, and fat-fed injected with STZ at the end of the 7-week period described above. Mice can be fasted for 4 hours before the experiments. In the first series of experiments, mice can be anesthetized with methoxyflurane (Pitman-Moor, Mundelein, IL) inhalation. Regular insulin (Sigma) can be injected intravenously ([IV] 0.1 U/kg body weight) through a tail vein, and blood can be collected 3, 6, 9, 12, and 15 minutes after the injection from a different tail vein. Plasma glucose concentrations can be determined on these samples, and the half-life (t½) of glucose disappearance from plasma can be calculated using WinNonlin (Scientific Consulting, Apex, NC), a pharmacokinetics/pharmacodynamics software program.

[1165] In the second series of experiments, mice can be anesthetized with intraperitoneal sodium pentobarbital (Sigma). The abdominal cavity is opened, and the main abdominal vein is exposed and catheterized with a 24-gauge IV catheter (Johnson-Johnson Medical, Arlington, TX). The

catheter is secured to muscle tissue adjacent to the abdominal vein, cut on the bottom of the syringe connection, and hooked to a prefilled PE50 plastic tube, which in turn is connected to a syringe with infusion solution. The abdominal cavity is then sutured closed. With this approach, there would be no blockage of backflow of the blood from the lower part of the body. Mice can be infused continuously with glucose (24.1 mg/kg/min) and insulin (10 mU/kg/min) at an infusion volume of 10 μL/min. Retro-orbital blood samples (70 μL each) can be taken 90, 105, 120, and 135 minutes after the start of infusion for measurement of plasma glucose and insulin concentrations. The mean of these four samples is used to estimate steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations for each animal.

[1166] Finally, experiments to evaluate the ability of the albumin fusion proteins, the therapeutic compositions of the instant application, either alone or in combination with any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus, to decrease plasma glucose can be performed in the following two groups of "NIDDM" mice models that are STZ-injected: (1) fat-fed C57BL/6J, and (2) fructose-fed C57BL/6J. Plasma glucose concentrations of the mice for these studies may range from 255 to 555 mg/dL. Mice are randomly assigned to treatment with either vehicle, albumin fusion therapeutics of the present invention either alone or in combination with any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus. A total of three doses can be administered. Tail vein blood samples can be taken for measurement of the plasma glucose concentration before the first dose and 3 hours after the final dose.

[1167] Plasma glucose concentrations can be determined using the Glucose Diagnostic Kit from Sigma (Sigma No. 315), an enzyme colorimetric assay. Plasma insulin levels can be determined using the Rat Insulin RIA Kit from Linco Research (#RI-13K; St. Charles, MO).

EXAMPLE 59: In vitro H4IIe -SEAP Reporter Assays Establishing Involvement in Insulin Action.

The Various H4IIe Reporters

[1168] *H4IIe/rMEP-SEAP*: The malic enzyme promoter isolated from rat (rMEP) contains a PPAR-gamma element which is in the insulin pathway. This reporter construct is stably transfected into the liver H4IIe cell-line.

[1169] *H4IIe/SREBP-SEAP*: The sterol regulatory element binding protein (SREBP-1c) is a transcription factor which acts on the promoters of a number of insulin-responsive genes, for example, fatty acid synthetase (FAS), and which regulates expression of key genes in fatty acid metabolism in fibroblasts, adipocytes, and hepatocytes. SREBP-1c, also known as the adipocyte determination and differentiation factor 1 (ADD-1), is considered as the primary mediator of insulin effects on gene expression in adipose cells. It's activity is modulated by the levels of insulin, sterols, and glucose. This reporter construct is stably transfected into the liver H4IIe cell-line.

[1170] *H4IIe/FAS-SEAP*: The fatty acid synthetase reporter constructs contain a minimal SREBP-responsive FAS promoter. This reporter construct is stably transfected into the liver H4IIe cell-line.

[1171] *H4IIe/PEPCK-SEAP*: The phosphoenolpyruvate carboxykinase (PEPCK) promoter is the primary site of hormonal regulation of PEPCK gene transcription modulating PEPCK activity. PEPCK catalyzes a committed and rate-limiting step in hepatic gluconeogenesis and must therefore be carefully controlled to maintain blood glucose levels within normal limits. This reporter construct is stably transfected into the liver H4IIe cell-line.

[1172] These reporter constructs can also be stably transfected into 3T3-L1 fibroblasts and L6 myoblasts. These stable cell-lines are then differentiated into 3T3-L1 adipocytes and L6 myotubes as previously described in Example 13. The differentiated cell-lines can then be used in the SEAP assay described below.

Growth and Assay Medium

[1173] The growth medium comprises 10% Fetal Bovine Serum (FBS), 10% Calf Serum, 1% NEAA, 1x penicillin/streptomycin, and 0.75 mg/mL G418 (for H4IIe/rFAS-SEAP and H4IIe/SREBP-SEAP) or 0.50 mg/mL G418 (for H4IIe/rMEP-SEAP). For H4IIe/PEPCK-SEAP, the growth medium consists of 10% FBS, 1% penicillin/streptomycin, 15 mM HEPES buffered saline, and 0.50 mg/mL G418.

[1174] The assay medium consists of low glucose DMEM medium (Life Technologies), 1% NEAA, 1x penicillin/streptomycin for the H4IIe/rFAS-SEAP, H4IIe/SREBP-SEAP, H4IIe/rMEP-SEAP reporters. The assay medium for H4IIe/PEPCK-SEAP reporter consists of 0.1% FBS, 1% penicillin/streptomycin, and 15 mM HEPES buffered saline.

Method

[1175] The 96-well plates are seeded at 75,000 cells/well in 100 μL/well of growth medium until cells in log growth phase become adherent. Cells are starved for 48 hours by replacing growth medium with assay medium, 200 μL/well. (For H4IIe/PEPCK-SEAP cells, assay medium containing 0.5 μM dexamethasone is added at 100 μL/well and incubated for approximately 20 hours). The assay medium is replaced thereafter with 100 μL/well of fresh assay medium, and a 50 μL aliquot of cell supernatant obtained from transfected cell-lines expressing the therapeutics of the subject invention (e.g., albumin fusion proteins of the invention and fragments and variants thereof) is added to the well. Supernatants from empty vector transfected cell-lines are used as negative control. Addition of 10 nM and/or 100 nM insulin to the wells is used as positive control. After 48 hours of incubation, the conditioned media are harvested and SEAP activity measured (Phospha-Light System protocol, Tropix #BP2500). Briefly, samples are diluted 1:4 in dilution buffer and incubated at 65 °C for 30 minutes to inactivate the endogenous non-placental form of SEAP. An aliquot of 50 μL of the diluted samples is mixed with 50 μL of SEAP Assay Buffer which contains a mixture of inhibitors active against the non-

placental SEAP isoenzymes and is incubated for another 5 minutes. An aliquot of 50 μL of CSPD chemiluminescent substrate which is diluted 1:20 in Emerald luminescence enhancer is added to the mixture and incubated for 15-20 minutes. Plates are read in a Dynex plate luminometer.

EXAMPLE 60: Transgenic Animals.

[1176] The albumin fusion proteins of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express fusion proteins of the invention in humans, as part of a gene therapy protocol.

[1177] Any technique known in the art may be used to introduce the polynucleotides encoding the albumin fusion proteins of the invention into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

[1178] Any technique known in the art may be used to produce transgenic clones containing polynucleotides encoding albumin fusion proteins of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

[1179] The present invention provides for transgenic animals that carry the polynucleotides encoding the albumin fusion proteins of the invention in all their cells, as well as animals which carry these polynucleotides in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide encoding the fusion protein of the invention be integrated into the chromosomal site of the endogenous gene corresponding to the Therapeutic protein portion or ablumin portion of the fusion protein of the invention, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

[1180] Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the polynucleotide encoding the fsuion protien of the invention has taken place. The level of mRNA expression of the polynucleotide encoding the fusion protein of the invention in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of fusion protein-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the fusion protein.

[1181] Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene (i.e., polynucleotide encoding an albumin fusion protein of the invention) on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of fusion proteins of the invention and the Therapeutic protein and/or albumin component of the fusion protein of the invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

EXAMPLE 61: Method of Treatment Using Gene Therapy-Ex Vivo.

[1182] One method of gene therapy transplants fibroblasts, which are capable of expressing an albumin fusion protein of the present invention, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

[1183] At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

[1184] pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

[1185] Polynucleotides encoding an albumin fusion protein of the invention can be generated using techniques known in the art amplified using PCR primers which correspond to the 5' and 3' end sequences and optionally having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

[1186] The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

[1187] Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether the albumin fusion protein is produced.

[1188] The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

EXAMPLE 62: Method of Treatment Using Gene Therapy - In Vivo.

[1189] Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences encoding an albumin fusion protein of the invention into an animal. Polynucleotides encoding albumin fusion proteins of the present invention may be operatively linked to (i.e., associated with) a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

[1190] The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[1191] The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, polynucleotides encoding albumin fusion proteins of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

[1192] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to

provide production of the desired polypeptide for periods of up to six months.

[1193] The polynucleotide construct can be delivered to the interstitial space of tissues within an animal, including muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[1194] For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[1195] The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

[1196] Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

[1197] After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for fusion protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

EXAMPLE 63: Biological Effects of Fusion Proteins of the Invention.

Astrocyte and Neuronal Assays.

[1198] Albumin fusion proteins of the invention can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an albumin fusion protein of the invention's activity on these cells.

[1199] Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA 83*:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of an albumin fusion protein of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

Fibroblast and endothelial cell assays.

[1200] Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal

microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test fusion protein of the invention proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE_2 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or fusion protein of the invention with or without IL-1α for 24 hours. The supernatants are collected and assayed for PGE_2 by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without an albumin fusion protein of the invention and/or IL-1α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

[1201] Human lung fibroblasts are cultured with FGF-2 or an albumin fusion protein of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with the fusion protein of the invention.

Cell proliferation based on [3H]thymidine incorporation

[1202] The following [3H]Thymidine incorporation assay can be used to measure the effect of a Therapeutic proteins, e.g., growth factor proteins, on the proliferation of cells such as fibroblast cells, epithelial cells or immature muscle cells.

[1203] Sub-confluent cultures are arrested in G1 phase by an 18 h incubation in serum-free medium. Therapeutic proteins are then added for 24 h and during the last 4 h, the cultures are labeled with [3H]thymidine, at a final concentration of 0.33 μM (25 Ci/mmol, Amersham, Arlington Heights, IL). The incorporated [3H]thymidine is precipitated with ice-cold 10% trichloroacetic acid for 24 h. Subsequently, the cells are rinsed sequentially with ice-cold 10% trichloroacetic acid and then with ice-cold water. Following lysis in 0.5 M NaOH, the lysates and PBS rinses (500 ml) are pooled, and the amount of radioactivity is measured.

Parkinson Models.

[1204] The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP^+) and released. Subsequently, MPP^+ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP^+ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotidamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

[1205] It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

[1206] Based on the data with FGF-2, an albumin fusion protein of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an albumin fusion protein of the invention is first examined in vitro in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm^2 on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days in vitro and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

[1207] Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if a therapeutic protein of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the fusion protein may be involved in Parkinson's Disease.

EXAMPLE 64: Pancreatic Beta-Cell Transplantation Combination Therapy.

[1208] Transplantation is a common form of treatment of autoimmune disease, especially when the target self tissue has been severely damaged.

For example, and not by way of limitation, pancreas transplantation and islet cell transplantation are common treatment options for IDDM (See, e.g., Stewart et al., Journal of Clinical Endocrinology & Metabolism 86 (3): 984-988 (2001); Brunicardi, Transplant. Proc. 28: 2138-40 (1996); Kendall & Robertson, Diabetes Metab. 22: 157-163 (1996); Hamano et al., Kobe J. Med. Sci. 42: 93-104 (1996); Larsen & Stratta, Diabetes Metab. 22: 139-146 (1996); and Kinkhabwala, et al., Am. J. Surg. 171: 516-520 (1996)). As with any transplantation method, transplantation therapies for autoimmune disease patients include treatments to minimize the risk of host rejection of the transplanted tissue. However, autoimmune disease involves the additional, independent risk that the pre-existing host autoimmune response which damaged the original self tissue will exert the same damaging effect on the transplanted tissue. Accordingly, the present invention encompasses methods and compositions for the treatment of autoimmune pancreatic disease using the albumin fusion proteins of the subject invetion in combination with immunomodulators/immunosuppressants in individuals undergoing transplantation therapy of the autoimmune disease.

[1209] In accordance with the invention, the albumin fusion-based compositions and formulations described above, are administered to prevent and treat damage to the transplanted organ, tissue, or cells resulting from the host individual's autoimmune response initially directed against the original self tissue. Administration may be carried out both prior and subsequent to transplantation in 2 to 4 doses each one week apart.

[1210] The following immunomodulators/immunosuppressants including, but not limited to, AI-401, CDP-571 (anti-TNF monoclonal antibody), CG-1088, Diamyd (diabetes vaccine), ICM3 (anti-ICAM-3 monoclonal antibody), linomide (Roquinimex), NBI-6024 (altered peptide ligand), TM-27, VX-740 (HMR-3480), caspase 8 protease inhibitors, thalidomide, hOKT3gamma1 (Ala-ala) (anti-CD3 monoclonal antibody), Oral Interferon-Alpha, oral lactobacillus, and LymphoStat-B™ can be used together with the albumin fusion therapeutics of the subject invention in islet cell or pancreas transplantation.

EXAMPLE 65:Identification and Cloning of VH and VL domains.

[1211] One method to identfy and clone VH and VL domains from cell lines expressing a particular antibody is to perform PCR with VH and VL specific primers on cDNA made from the antibody expressing cell lines. Briefly, RNA is isolated from the cell lines and used as a template for RT-PCR designed to amplify the VH and VL domains of the antibodies expressed by the EBV cell lines. Cells may be lysed in the TRIzol® reagent (Life Technologies, Rockville. MD) and extracted with one fifth volume of chloroform. After addition of chloroform, the solution is allowed to incubate at room temperature for 10 minutes, and the centrifuged at 14,000 rpm for 15 minutes at 4°C in a tabletop centrifuge. The supernatant is collected and RNA is precipitated using an equal volume of isopropanol. Precipitated RNA is pelleted by centrifuging at 14,000 rpm for 15 minutes at 4°C in a tabletop centrifuge. Following centrifugation, the supernatant is discarded and washed with 75% ethanol. Follwing washing, the RNA is centrifuged again at 800 rpm for 5 minutes at 4°C. The supernatant is discarded and the pellet allowed to air dry. RNA is the dissolved in DEPC water and heated to 60°C for 10 minutes. Quantities of RNA can determined using optical density measurements.

[1212] cDNA may be synthesized, according to methods well-known in the art, from 1.5-2.5 micrograms of RNA using reverse transciptase and random hexamer primers. cDNA is then used as a template for PCR amplification of VH and VL domains. Primers used to amplify VH and VL genes are shown in Table 7. Typically a PCR reaction makes use of a single 5' primer and a single 3' primer. Sometimes, when the amount of available RNA template is limiting, or for greater efficiency, groups of 5' and/or 3' primers may be used. For example, sometimes all five VH-5' primers and all JH3' primers are used in a single PCR reaction. The PCR reaction is carried out in a 50 microliter volume containing 1X PCR buffer, 2mM of each dNTP, 0.7 units of High Fidelity Taq polymerse, 5' primer mix, 3' primer mix and 7.5 microliters of cDNA. The 5' and 3' primer mix of both VH and VL can be made by pooling together 22 pmole and 28 pmole, respectively, of each of the individual primers. PCR conditions are: 96°C for 5 minutes; followed by 25 cycles of 94°C for 1 minute, 50°C for 1 minute, and 72°C for 1 minute; followed by an extension cycle of 72°C for 10 minutes. After the reaction is completed, sample tubes are stored 4°C.

Table 7: Primer Sequences Used to Amplify VH and VL domains.

Primer name	SEQ ID NO	Primer Sequence (5'-3')
VH Primers		
Hu VH1-5'	62	CAGGTGCAGCTGGTGCAGTCTGG
Hu VH2-5'	63	CAGGTCAACTTAAGGGAGTCTGG
Hu VH3-5'	64	GAGGTGCAGCTGGTGGAGTCTGG
Hu VH4-5'	65	CAGGTGCAGCTGCAGGAGTCGGG
Hu VH5-5'	66	GAGGTGCAGCTGTTGCAGTCTGC
Hu VH6-5'	67	CAGGTACAGCTGCAGCAGTCAGG
Hu JH1,2-5'	68	TGAGGAGACGGTGACCAGGGTGCC
Hu JH3-5'	69	TGAAGAGACGGTGACCATTGTCCC
Hu JH4,5-5'	70	TGAGGAGACGGTGACCAGGGTTCC
Hu JH6-5'	71	TGAGGAGACGGTGACCGTGGTCCC

VL Primers

Hu Vkappa1-5'	72	GACATCCAGATGACCCAGTCTCC
Hu Vkappa2a-5'	73	GATGTTGTGATGACTCAGTCTCC
Hu Vkappa2b-5'	74	GATATTGTGATGACTCAGTCTCC
Hu Vkappa3-5'	75	GAAATTGTGTTGACGCAGTCTCC
Hu Vkappa4-5'	76	GACATCGTGATGACCCAGTCTCC
Hu Vkappa5-5'	77	GAAACGACACTCACGCAGTCTCC
Hu Vkappa6-5'	78	GAAATTGTGCTGACTCAGTCTCC
Hu Vlambda1-5'	79	CAGTCTGTGTTGACGCAGCCGCC
Hu Vlambda2-5'	80	CAGTCTGCCCTGACTCAGCCTGC
Hu Vlambda3-5'	81	TCCTATGTGCTGACTCAGCCACC
Hu Vlambda3b-5'	82	TCTTCTGAGCTGACTCAGGACCC
Hu Vlambda4-5'	83	CACGTTATACTGACTCAACCGCC
Hu Vlambda5-5'	84	CAGGCTGTGCTCACTCAGCCGTC
Hu Vlambda6-5'	85	AATTTTATGCTGACTCAGCCCCA
Hu Jkappa1-3'	86	ACGTTTGATTTCCACCTTGGTCCC
Hu Jkappa2-3'	87	ACGTTTGATCTCCAGCTTGGTCCC
Hu Jkappa3-3'	88	ACGTTTGATATCCACTTTGGTCCC
Hu Jkappa4-3'	89	ACGTTTGATCTCCACCTTGGTCCC
Hu Jkappa5-3'	90	ACGTTTAATCTCCAGTCGTGTCCC
Hu Jlambda1-3'	91	CAGTCTGTGTTGACGCAGCCGCC
Hu Jlambda2-3'	92	CAGTCTGCCCTGACTCAGCCTGC
Hu Jlambda3--3'	93	TCCTATGTGCTGACTCAGCCACC
Hu Jlambda3b-3'	94	TCTTCTGAGCTGACTCAGGACCC
Hu Jlambda4-3'	95	CACGTTATACTGACTCAACCGCC
Hu Jlambda5-3'	96	CAGGCTGTGCTCACTCAGCCGTC
Hu Jlambda6-3'	97	AATTTTATGCTGACTCAGCCCCA

PCR samples are then electrophoresed on a 1.3% agarose gel. DNA bands of the expected sizes (~506 base pairs for VH domains, and 344 base pairs for VL domains) can be cut out of the gel and purified using methods well known in the art. Purified PCR products can be ligated into a PCR cloning vector (TA vector from Invitrogen Inc., Carlsbad, CA). Individual cloned PCR products can be isolated after transfection of E. coli and blue/white color selection. Cloned PCR products may then be sequenced using methods commonly known in the art.

[1213] The PCR bands containing the VH domain and the VL domains can also be used to create full-length Ig expression vectors. VH and VL domains can be cloned into vectors containing the nucleotide sequences of a heavy (e.g., human IgG1 or human IgG4) or light chain (human kappa or human lambda) constant regions such that a complete heavy or light chain molecule could be expressed from these vectors when transfected into an appropriate host cell. Further, when cloned heavy and light chains are both expressed in one cell line (from either one or two vectors), they can assemble into a complete functional antibody molecule that is secreted into the cell culture medium. Methods using polynucleotides encoding VH and VL antibody domain to generate expression vectors that encode complete antibody molecules are well known within the art.

EXAMPLE 66: Preparation of HA-cytokine or HA-growth factor fusion proteins (such as NGF, BDNFa, BDNFb and BDNFc).

[1214] The cDNA for the cytokine or growth factor of interest, such as NGF, can be isolated by a variety of means including from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for all of these proteins are known and available. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. NGF (or other cytokine) cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA, or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines, a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

EXAMPLE 67: Preparation of HA-IFN fusion proteins (such as IFNα).

[1215] The cDNA for the interferon of interest such as IFNα can be isolated by a variety of means including but not exclusively, from cDNA

libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for interferons, such as IFNα are known and available, for instance, in U.S. Patents 5,326,859 and 4,588,585, in EP 32 134, as well as in public databases such as GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used to clone the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus of the HA sequence, with or without the use of a spacer sequence. The IFNα (or other interferon) cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

Maximum protein recovery from vials

[1216] The albumin fusion proteins of the invention have a high degree of stability even when they are packaged at low concentrations. In addition, in spite of the low protein concentration, good fusion-protein recovery is observed even when the aqueous solution includes no other protein added to minimize binding to the vial walls. The recovery of vial-stored HA-IFN solutions was compared with a stock solution. 6 or 30 μg/ml HA-IFN solutions were placed in vials and stored at 4°C. After 48 or 72 hrs a volume originally equivalent to 10 ng of sample was removed and measured in an IFN sandwich ELISA. The estimated values were compared to that of a high concentration stock solution. As shown, there is essentially no loss of the sample in these vials, indicating that addition of exogenous material such as albumin is not necessary to prevent sample loss to the wall of the vials

In vivo stability and bioavailability of HA-α-IFN fusions

[1217] To determine the in vivo stability and bioavailability of a HA-α-IFN fusion molecule, the purified fusion molecule (from yeast) was administered to monkeys. Pharmaceutical compositions formulated from HA-α-IFN fusions may account for the extended serum half-life and bioavailability. Accordingly, pharmaceutical compositions may be formulated to contain lower dosages of alpha-interferon activity compared to the native alpha-interferon molecule.

[1218] Pharmaceutical compositions containing HA-α-IFN fusions may be used to treat or prevent disease in patients with any disease or disease state that can be modulated by the administration of α-IFN. Such diseases include, but are not limited to, hairy cell leukemia, Kaposi's sarcoma, genital and anal warts, chronic hepatitis B, chronic non-A, non-B hepatitis, in particular hepatitis C, hepatitis D, chronic myelogenous leukemia, renal cell carcinoma, bladder carcinoma, ovarian and cervical carcinoma, skin cancers, recurrent respirator papillomatosis, non-Hodgkin's and cutaneous T-cell lymphomas, melanoma, multiple myeloma , AIDS, multiple sclerosis, gliobastoma, etc. (see Interferon Alpha, In: AHFS Drug Information, 1997.

[1219] Accordingly, the invention includes pharmaceutical compositions containing a HA-α-IFN fusion protein, polypeptide or peptide formulated with the proper dosage for human administration. The invention also includes methods of treating patients in need of such treatment comprising at least the step of administering a pharmaceutical composition containing at least one HA-α-IFN fusion protein, polypeptide or peptide.

Bifunctional HA-α-IFN fusions

[1220] A HA-α-IFN expression vector may be modified to include an insertion for the expression of bifunctional HA-α-IFN fusion proteins. For instance, the cDNA for a second protein of interest may be inserted in frame downstream of the "rHA-IFN" sequence after the double stop codon has been removed or shifted downstream of the coding sequence.

[1221] In one version of a bifunctional HA-α-IFN fusion protein, an antibody or fragment against B-lymphocyte stimulator protein (GenBank Acc 4455139) or polypeptide may be fused to one end of the HA component of the fusion molecule. This bifunctional protein is useful for modulating any immune response generated by the α-IFN component of the fusion.

EXAMPLE 68: Preparation of HA-hormone fusion protein

[1222] The cDNA for the hormone of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for all of these proteins are known and available, for instance, in public databases such as GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The hormone cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

EXAMPLE 69: Preparation of HA-soluble receptor or HA-binding protein fusion protein.

[1223] The cDNA for the soluble receptor or binding protein of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for all of these proteins are known and available, for instance, in GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The receptor cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

EXAMPLE 70: Preparation of HA-growth factors.

[1224] The cDNA for the growth factor of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods (see GenBank Acc. No.NP_000609). The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The growth factor cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

EXAMPLE 71: Preparation of HA-single chain antibody fusion proteins.

[1225] Single chain antibodies are produced by several methods including but not limited to: selection from phage libraries, cloning of the variable region of a specific antibody by cloning the cDNA of the antibody and using the flanking constant regions as the primer to clone the variable region, or by synthesizing an oligonucleotide corresponding to the variable region of any specific antibody. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The cell cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast.

[1226] In fusion molecules of the invention, the V_H and V_L can be linked by one of the following means or a combination thereof: a peptide linker between the C-terminus of the V_H and the N-terminus of the V_L; a Kex2p protease cleavage site between the V_H and V_L such that the two are cleaved apart upon secretion and then self associate; and cystine residues positioned such that the V_H and V_L can form a disulphide bond between them to link them together. An alternative option would be to place the V_H at the N-terminus of HA or an HA domain fragment and the V_L at the C-terminus of the HA or HA domain fragment.

[1227] The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines. The antibody produced in this manner can be purified from media and tested for its binding to its antigen using standard immunochemical methods.

EXAMPLE 72: Preparation of HA-cell adhesion molecule fusion proteins.

[1228] The cDNA for the cell adhesion molecule of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. . The nucleotide sequences for the known cell adhesion molecules are known and available, for instance, in GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The cell adhesion molecule cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

EXAMPLE 73: Preparation of inhibitory factors and peptides as HA fusion proteins (such as HA-antiviral, HA-antibiotic, HA-enzyme inhibitor and HA-anti-allergic proteins).

[1229] The cDNA for the peptide of interest such as an antibiotic peptide can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The peptide cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

EXAMPLE 74: Preparation of targeted HA fusion proteins.

[1230] The cDNA for the protein of interest can be isolated from cDNA library or can be made synthetically using several overlapping oligonucleotides using standard molecular biology methods. The appropriate nucleotides can be engineered in the cDNA to form convenient restriction sites and also allow the attachment of the protein cDNA to albumin cDNA. Also a targeting protein or peptide cDNA such as single chain antibody or peptides, such as nuclear localization signals, that can direct proteins inside the cells can be fused to the other end of albumin. The protein of interest and the targeting peptide is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA which allows the fusion with albumin cDNA. In this manner both N- and C-terminal end of albumin are fused to other proteins. The fused cDNA is then excised from pPPC0005 and is inserted into a plasmid such as pSAC35 to allow the expression of the albumin fusion protein in yeast. All the above procedures can be performed using standard methods in molecular biology. The albumin fusion protein secreted from yeast can be collected and purified from the media and tested for its biological activity and its targeting activity using appropriate biochemical and biological tests.

EXAMPLE 75: Preparation of HA-enzymes fusions.

[1231] The cDNA for the enzyme of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The enzyme cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA, or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

EXAMPLE 76: Construct ID 2053, IFNb-HSA, Generation.

[1232] Construct ID 2053, pEE12.1:IFNb.HSA, comprises DNA encoding an IFNb albumin fusion protein which has the full-length IFNb protein including the native IFNb leader sequence fused to the amino-terminus of the mature form of HSA in the NS0 expression vector pEE12.1.

Cloning of IFNb cDNA

[1233] The polynucleotide encoding IFNb was PCR amplified using primers IFNb-1 and IFNb-2, described below, cut with *Bam* HI/*Cla* I, and ligated into *Bam* HI/*Cla* I cut pC4:HSA, resulting in construct 2011. The *Eco* RI/*Eco* RI fragment from Construct ID # 2011 was subcloned into the *Eco* RI site of pEE12.1 generating construct ID #2053 which which comprises DNA encoding an albumin fusion protein containing the leader sequence and the mature form of IFNb, followed by the mature HSA protein.

[1234] Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the full-length of IFNb, IFNb-1 and IFNb-2, were synthesized:

IFNb-1: 5'-GCGCGGATCCGAATT*CCGCCGCCATG*ACCAACAAGTGTCTCCTCCAAATTGCTCTCCTGTTGTGCTT CTCCACTACAGCTCTTTCCATGAGCTACAACTTGCTTGG-3' (SEQ ID NO:107)

IFNb-2: 5'-GCGCGCATCGATGAGCAACCTCACTCTTGTGTGCATCGTTTCGGA GGTAACCTGT-3' (SEQ ID NO:108)

[1235] The IFNb-1 primer incorporates a *Bam* HI cloning site (shown underlined), an *Eco* RI cloning site, and a Kozak sequence (shown in italics), followed by 80 nucleotides encoding the first 27 amino acids of the full-length form of IFNb. In IFNb-2, the *Cla* I site (shown underlined) and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein (SEQ ID NO:1) and the last 18 nucleotides are the reverse complement of DNA encoding the last 6 amino acid residues of IFNb (see Example 2). A PCR amplimer was generated using these primers, purified, digested with *Bam* HI and *Cla* I restriction enzymes, and cloned into the *Bam* HI and *Cla* I sites of the pC4:HSA vector. After the sequence was confirmed, an *Eco* RI fragment containing the IFNb albumin fusion protein expression cassette was subcloned into *Eco* RI digested pEE12.1.

[1236] Further, analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing can confirm the presence of the expected IFNb sequence (see below).

[1237] IFNb albumin fusion proteins of the invention preferably comprise the mature form of HSA, i.e., Asp-25 to Leu-609, fused to either the N- or C- terminus of the mature form of IFNb, i.e., Met-22 to Asn-187. In one embodiment of the invention, IFNb albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a further preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature IFNb albumin fusion protein is secreted directly into the culture medium. IFNb albumin fusion proteins of the invention may comprise heterologous signal sequences including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In a preferred embodiment, IFNb albumin fusion proteins of the invention comprise the native IFNb. In further preferred embodiments, the IFNb albumin fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

Expression and Purification of Construct ID 2053.

Expression in murine myeloma NS0 cell-lines.

[1238] Construct ID # 2053, pEE12.1:IFNb-HSA, was electroporated into NS0 cells by methods known in the art (see Example 6).

Purification from NS0 cell supernatant.

[1239] Purification of IFNb-HSA from NS0 cell supernatant may involve Q-Sepharose anion exchange chromatography at pH 7.4 using a NaCl gradient from 0 to 1 M in 20 mM Tris-HCl, followed by Poros PI 50 anion exchange chromatography at pH 6.5 with a sodium citrate gradient from 5 to 40 mM, and diafiltrating for 6 DV into 10 mM citrate, pH 6.5 and 140 mM NaCl, the final buffer composition. N-terminal sequencing should yield the sequence MSYNLL which is the amino terminus of the mature form of IFNb. The protein has an approximate MW of 88.5 kDa.

[1240] For larger scale purification, e.g., 50 L of NS0 cell supernatant can be concentrated into ~8 to 10 L. The concentrated sample can then be passed over the Q-Sepharose anion exchange column (10 x 19 cm, 1.5 L) at pH 7.5 using a step elution consisting of 50 mM NaOAc, pH 6.0 and 150 mM NaCl. The eluted sample can then be virally inactivated with 0.75% Triton-X 100 for 60 min at room temperature. SDR-Reverse Phase chromatography (10 cm x 10 cm, 0.8 L) can then be employed at pH 6.0 with 50 mM NaOAc and 150 mM NaCl, or alternatively, the sample can be passed over an SP-sepharose column at pH 4.8 using a step elution of 50 mM NaOAc, pH 6.0, and 150 mM NaCl. DV 50 filtration would follow to remove any viral content. Phenyl-650M chromatography (20 cm x 12 cm, 3.8 L) at pH 6.0 using a step elution consisting of 350 mM $(NH_4)_2SO_4$ and 50 mM NaOAc, or alternatively consisting of 50 mM NaOAc pH 6.0, can follow. Diafiltration for 6-8 DV will allow for buffer exchange into the desired final formulation buffer of either 10 mM Na_2HPO_4 + 58 mM sucrose + 120 mM NaCl, pH 7.2 or 10 mM citrate, pH 6.5, and 140 mM NaCl or 25 mM Na_2HPO_4, 100 mM NaCl, pH 7.2.

The activity of IFNb can be assayed using an in vitro ISRE-SEAP assay.

[1241] All type I Interferon proteins signal through a common receptor complex and a similar Jak/STAT signaling pathway that culminates in the activation of Interferon, "IFN", responsive genes through the Interferon Sequence Responsive Element, "ISRE". A convenient assay for type I IFN activity is a promoter-reporter based assay system that contains multiple copies of the ISRE element fused to a downstream reporter gene. A stable HEK293 cell-line can be generated and contains a stably integrated copy of an ISRE-SEAP reporter gene that is extremely sensitive to type I IFNs and displays linearity over 5 logs of concentration.

Method of Screening of IFNb-HSA NS0 stable clones.

[1242] Construct 2053 was electroporated into NS0 cells as described in Example 6. The NS0 cells transfected with construct ID # 2053 were screened for activity by testing conditioned growth media in the ISRE-SEAP assay. The ISRE-SEAP/293F reporter cells were plated at 3 x 10^4 cell/well in 96-well, poly-D-lysine coated, plates, one day prior to treatment. Reporter cells were treated with various dilutions (including but not limited to 1:500 and 1:5000) of conditioned supernatant or purified preparations of IFNb albumin fusion protein encoded by construct ID 2053 or rhIFNb as a control. The reporter cells were then incubated for 24 hours prior to removing 40 μL for use in the SEAP Reporter Gene Chemiluminescent Assay (Roche catalog # 1779842). Recombinant human Interferon beta, "rhIFNb" (Biogen), was used as a positive control.

Result

[1243] The purified preparation of NS0 expressed IFNb-HSA had a greater EC50 of 9.3 x 10^{-9} g/mL than rhIFNb (Biogen) which had an EC50 of 1.8 x 10^{-10} g/mL (see Figure 4).

In vivo induction of OAS by an Interferon.

Method

[1244] The OAS enzyme, 2'-5'- OligoAdenylate Synthetase, is activated at the transcriptional level by interferon in response to antiviral infection. The effect of interferon constructs can be measured by obtaining blood samples from treated monkeys and analyzing these samples for transcriptional activation of two OAS mRNA, p41 and p69. A volume of 0.5 mL of whole blood can be obtained from 4 animals per group at 7 different time points, day 0, day 1, day 2, day 4, day 8, day 10, and day 14 per animal. The various groups may include injection of vehicle control,

intravenous and/or subcutaneous injection of either 30 μg/kg and/or 300 μg/kg IFN albumin fusion protein on day 1, and subcutaneous injection of 40 μg/kg of Interferon alpha (Schering-Plough) as a positive control on days 1, 3, and 5. The levels of the p41 and the p69 mRNA transcripts can be determined by real-time quantitative PCR (Taqman) using probes specific for p41-OAS and p69-OAS. OAS mRNA levels can be quantitated relative to 18S ribosomal RNA endogenous control.

In vivo induction of OAS by Interferon beta albumin fusion encoded by construct ID 2053.

Method

[1245] The activity of the HSA-IFNb fusion protein encoded by construct 2053 can be assayed in the *in vivo* OAS assay as previously described above under subsection heading, "*In vivo* induction of OAS by an Interferon".

EXAMPLE 77: Indications for IFNb albumin fusion proteins.

[1246] IFN beta albumin fusion proteins (including, but not limited to, those encoded by construct 2053) can be used to treat, prevent, ameliorate and/or detect multiple sclerosis. Other indications include, but are not limited to Viral infections including Severe Acute Respiratory Syndrome (SARS) and other coronavirus infections; filoviruses, including but not limited to Ebola viruses and Marburg virus; Arenaviruses, including but not limited to Pichende virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus; and lymphocytic choriomeningitis virus (LCMV); Bunyaviruses, including but not limited to Punta toro virus, Crimean-Congo hemorrhagic fever virus, sandfly fever viruses, Rift Valley fever virus, La Crosse virus, and hantaviruses; Flaviviruses, including but not limited to Yellow Fever, Banzi virus, West Nile virus, Dengue viruses, Japanese Encephalitis virus, Tick-borne encephalitis, Omsk Hemorrhagic Fever, and Kyasanur Forest Disease virus; Togaviruses, including but not limited to Venezuelan, eastern, and western equine encephalitis viruses, Ross River virus, and Rubella virus; Orthopox viruses, including but not limited to Vaccinia, Cowpox, Smallpox, and Monkeypox; Herpesviruses; FluA/B; Respiratory Sincytial virus (RSV); paraflu; measles; rhinoviruses; adenoviruses; Semliki Forest virus; Viral Hemorrhagic fevers; Rhabdoviruses; Paramyxoviruses, including but not limited to Nipah virus and Hendra virus; and other viral agents identified by the U.S. Centers for Disease Control and Prevention as high-priority disease agents (*i.e.*, Category A, B, and C agents; see, *e.g.*, Moran, Emerg. Med. Clin. North. Am. 2002; 20(2):311-30 and Darling et al., Emerg. Med. Clin. North Am. 2002;20(2):273-309).

EXAMPLE 78: Construct ID 2249, IFNa2-HSA, Generation.

[1247] Construct ID 2249, pSAC35:IFNa2.HSA, comprises DNA encoding an IFNa2 albumin fusion protein which has the HSA chimeric leader sequence, followed by the mature form of IFNa2 protein, i.e., C1-E165, fused to the amino-terminus of the mature form of HSA in the yeast *S. cerevisiae* expression vector pSAC35.

Cloning of IFNa2 cDNA

[1248] The polynucleotide encoding IFNa2 was PCR amplified using primers IFNa2-1 and IFNa2-2, described below. The PCR amplimer was cut with *Sal I/Cla* I, and ligated into *Xho I/Cla* I cut pScCHSA. Construct ID #2249 encodes an albumin fusion protein containing the chimeric leader sequence of HSA, the mature form of IFNa2, followed by the mature HSA protein.

[1249] Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the mature form of IFNa2, IFNa2-1 and IFNa2-2, were synthesized:

IFNa2-1: 5'-CGCGCGCGTCGACAAAAGATGTGATCTGCCTCAAACCCACA-3' (SEQ ID NO:109)

IFNa2-2: 5'-GCGCGCATCGATGAGCAACCTCACTCTTGTGTGCATCTTCCTTACTTCTTAAACTTTCT-3' (SEQ ID NO:110)

[1250] The IFNa2-1 primer incorporates a *Sal* I cloning site (shown underlined), nucleotides encoding the last three amino acid residues of the chimeric HSA leader sequence, as well as 22 nucleotides (shown in bold) encoding the first 7 amino acid residues of the mature form of IFNa2. In IFNa2-2, the *Cla* I site (shown underlined) and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein and the last 22 nucleotides (shown in bold) are the reverse complement of DNA encoding the last 7 amino acid residues of IFNa2 (see Example 2). A PCR amplimer of IFNa2-HSA was generated using these primers, purified, digested with *Sal* I and *Cla* I restriction enzymes, and cloned into the *Xho* I and *Cla* I sites of the pScCHSA vector. After the sequence was confirmed, the expression cassette encoding this IFNa2 albumin fusion protein was subcloned into *Not* I digested pSAC35.

[1251] Further, analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing can confirm the presence of the expected IFNa2 sequence (see below).

[1252] Other IFNa2 albumin fusion proteins using different leader sequences have been constructed by methods known in the art (see Example 2). Examples of the various leader sequences include, but are not limited to, invertase "INV" (constructs 2343 and 2410) and mating alpha factor "MAF" (construct 2366). These IFNa2 albumin fusion proteins can be subcloned into mammalian expression vectors such as pC4 (constructs 2382) and pEE12.1 as described previously (see Example 5). IFNa2 albumin fusion proteins with the therapeutic portion fused C-terminus to HSA can also be constructed (construct 2381).

[1253] IFNa2 albumin fusion proteins of the invention preferably comprise the mature form of HSA, i.e., Asp-25 to Leu-609, fused to either the N- or C- terminus of the mature form of IFNa2, i.e., Cys-1 to Glu-165. In one embodiment of the invention, IFNa2 albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression.

In a further preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature IFNa2 albumin fusion protein is secreted directly into the culture medium. IFNa2 albumin fusion proteins of the invention may comprise heterologous signal sequences including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In a preferred embodiment, IFNa2 albumin fusion proteins of the invention comprise the native IFNa2. In further preferred embodiments, the IFNa2 albumin fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

Expression and Purification of Construct ID 2249.

Expression in yeast S. cerevisiae.

[1254] Transformation of construct 2249 into yeast *S. cerevisiae* strain BXP10 was carried out by methods known in the art (see Example 3). Cells can be collected at stationary phase after 72 hours of growth. Supernatants are collected by clarifying cells at 3000g for 10 min. Expression levels are examined by immunoblot detection with anti-HSA serum (Kent Laboratories) or as the primary antibody. The IFNa2 albumin fusion protein of approximate molecular weight of 88.5 kDa can be obtained.

Purification from yeast S. cerevisiae cell supernatant.

[1255] The cell supernatant containing IFNa2 albumin fusion protein expressed from construct ID #2249 in yeast *S. cerevisiae* cells can be purified either small scale over a Dyax peptide affinity column (see Example 4) or large scale by following 5 steps: diafiltration, anion exchange chromatography using DEAE-Sepharose Fast Flow column, hydrophobic interaction chromatography (HIC) using Butyl 650S column, cation exchange chromatography using an SP-Sepharose Fast Flow column or a Blue-Sepharose chromatography, and high performance chromatography using Q-sepharose high performance column chromatography (see Example 4). The IFNa2 albumin fusion protein may elute from the DEAE-Sepharose Fast Flow column with 100 – 250 mM NaCl, from the SP-Sepharose Fast Flow column with 150 – 250 mM NaCl, and from the Q-Sepharose High Performance column at 5 – 7.5 mS/cm. N-terminal sequencing should yield the sequence CDLPQ (SEQ ID NO:98) which corresponds to the mature form of IFNa2.

The activity of IFNa2 can be assayed using an in vitro ISRE-SEAP assay.

Method

[1256] The IFNa2 albumin fusion protein encoded by construct ID # 2249 can be tested for activity in the ISRE-SEAP assay as previously described in Example 76. Briefly, conditioned yeast supernatants were tested at a 1:1000 dilution for their ability to direct ISRE signal transduction on the ISRE-SEAP/293F reporter cell-line. The ISRE-SEAP/293F reporter cells were plated at 3×10^4 cell/well in 96-well, poly-D-lysine coated, plates, one day prior to treatment. The reporter cells were then incubated for 18 or 24 hours prior to removing 40 µL for use in the SEAP Reporter Gene Chemiluminescent Assay (Roche catalog # 1779842). Recombinant human Interferon beta, "rhIFNb" (Biogen), was used as a positive control.

Result

[1257] The purified preparation of IFNa2-HSA demonstrated a relatively linear increase in the ISRE-SEAP assay over concentrations ranging from 10^{-1} to 10^{1} ng/mL (see Figure 5) or 10^{-10} to 10^{-8} ng/mL (see Figure 6).

In vivo induction of OAS by Interferon alpha fusion encoded by construct ID 2249.

Method

[1258] The OAS enzyme, 2'-5'- OligoAdenylate Synthetase, is activated at the transcriptional level by interferon in response to antiviral infection. The effect of interferon constructs can be measured by obtaining blood samples from treated monkeys and analyzing these samples for transcriptional activation of two OAS mRNA, p41 and p69. A volume of 0.5 mL of whole blood was obtained from 4 animals per group at 7 different time points, day 0, day 1, day 2, day 4, day 8, day 10, and day 14 per animal. The various groups include vehicle control, intravenous injection of 30 µg/kg HSA-IFN on day 1, subcutaneous injection of 30 µg/kg of HSA-IFN on day 1, subcutaneous injection of 300 µg/kg of HSA-IFN on day 1, and subcutaneous injection of 40 µg/kg of Interferon alpha (Schering-Plough) as a positive control on days 1, 3, and 5. The levels of the p41 and the p69 mRNA transcripts were determined by real-time quantitative PCR (Taqman) using probes specific for p41-OAS and p69-OAS. OAS mRNA levels were quantitated relative to 18S ribosomal RNA endogenous control. The albumin fusion encoded by construct 2249 can be subjected to similar experimentation.

Results

[1259] A significant increase in mRNA transcript levels for both p41 and p69 OAS was observed in HSA-interferon treated monkeys in contrast to IFNa treated monkeys (see Figure 7 for p41 data). The effect lasted nearly 10 days.

EXAMPLE 79: Indications for IFNa2 Albumin Fusion Proteins.

[1260] IFN alpha albumin fusion protein (including, but not limited to, those encoded by constructs 2249, 2343, 2410, 2366, 2382, and 2381) can be used to treat, prevent, ameliorate, and/or detect multiple sclerosis. Other indications include, but are not limited to viral infections including Severe Acute Respiratory Syndrome (SARS) and other coronavirus infections; filoviruses, including but not limited to Ebola viruses and Marburg

virus; Arenaviruses, including but not limited to Pichende virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus; and lymphocytic choriomeningitis virus (LCMV); Bunyaviruses, including but not limited to Punta toro virus, Crimean-Congo hemorrhagic fever virus, sandfly fever viruses, Rift Valley fever virus, La Crosse virus, and hantaviruses; Flaviviruses, including but not limited to Yellow Fever, Banzi virus, West Nile virus, Dengue viruses, Japanese Encephalitis virus, Tick-borne encephalitis, Omsk Hemorrhagic Fever, and Kyasanur Forest Disease virus; Togaviruses, including but not limited to Venezuelan, eastern, and western equine encephalitis viruses, Ross River virus, and Rubella virus; Orthopox viruses, including but not limited to Vaccinia, Cowpox, Smallpox, and Monkeypox; Herpesviruses; FluA/B; Respiratory Sincytial virus (RSV); paraflu; measles; rhinoviruses; adenoviruses; Semliki Forest virus; Viral Hemorrhagic fevers; Rhabdoviruses; Paramyxoviruses, including but not limited to Nipah virus and Hendra virus; and other viral agents identified by the U.S. Centers for Disease Control and Prevention as high-priority disease agents (*i.e.*, Category A, B, and C agents; see, *e.g.*, Moran, Emerg. Med. Clin. North. Am. 2002; 20(2):311-30 and Darling et al., Emerg. Med. Clin. North Am. 2002;20(2):273-309).

[1261] Preferably, the IFNα-albumin fusion protein or IFN hybrid fusion protein is administered in combination with a CCR5 antagonist, further in association with at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with an anti-HIV drug therapy, e.g., HAART, for preparation of a medicament for the treatment of HIV-1 infections, HCV, or HIV-1 and HCV co-infections in treatment-naïve as well as treatment-experienced adult and pediatric patients.

Example 80: Construct ID # 3691, BNP-HSA, Generation.

[1262] Construct ID # 3691, pC4:SPCON.BNP1-32/HSA, comprises DNA encoding a BNP albumin fusion protein which has a consensus leader sequence, secrecon, followed by the processed, active BNP peptide (amino acids 1-32) fused to the amino-terminus of the mature form of HSA in the mammalian expression vector pC4.

Cloning of BNP cDNA for construct 3691

[1263] The polynucleotide encoding BNP was PCR amplified using primers BNP-1 and BNP-2, described below, cut with *Bam* HI/*Cla* I, and ligated into *Bam* HI/*Cla* I cut pC4:HSA resulting in construct ID # 3691. Construct ID # 3691 encodes an albumin fusion protein containing a consensus leader sequence (SEQ ID No:111) and the processed, active form of BNP, followed by the mature HSA protein (see SEQ ID No:321 for construct 3691 in Table 2).

[1264] Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the active, processed form of BNP, BNP-1 and BNP-2, were synthesized:

BNP-1: 5'-GAGCGCGGATCCAAGCTTCCGCCATC*ATGTGGTGGCGCCTGTGGTGGCTGCTGCTGCTGCTGCTGCTGTG GCCCATGGTGTGGGCC*AGCCCCAAGCTGGTGCAAGG -3' (SEQ ID NO:463)

BNP-2: 5'-AGTCCCATCGATGAGCAACCTCACTCTTGTGTGCATCATGCCGCCTCAGCACTTTGC-3' (SEQ ID NO:464).

[1265] BNP-1 incorporates a *Bam* HI cloning site (underlined), polynucleotides encoding a consensus leader sequence (SEQ ID No:111) (italicized), and polynucleotides encoding the first seven amino acid sequence of BNP (bolded). In BNP-2, the underlined sequence is a *Cla* I site, and the polynucleotides that follow it contains the reverse complement of DNA encoding the last 6 amino acids of BNP (bolded) and the first 10 amino acids of the mature HSA protein. Using these two primers the BNP protein was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

[1266] The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bam* HI and *Cla* I. After further purification of the *Bam* HI-*Cla* I fragment by gel electrophoresis, the product was cloned into *Bam* HI /*Cla* I digested pC4:HSA to produce construct ID # 3691. The expression construct was sequence verified.

Expression and Purification of Construct ID 3691.

Expression in 293F cells.

[1267] Construct ID # 3691, pC4:SPCON.BNP1-32/HSA, was transfected into 293F cells by methods known in the art (see Example 6).

Purification from 293F cell supernatant.

[1268] Two liters of supernatant were collected 3 days post-transfection. The recombinant protein was captured by 5 ml Blue Sepharose CL-6B column (Amersham Biosciences, Piscataway, NJ, USA) and eluted by 2 M NaCl. The material was bound to HiPrep 16/10 Phenyl FF (high sub) column and eluted by 20 mM MES, pH 6.7. BNP-HSA was further purified by hydroxyapatite column chromatography in sodium phosphate buffer gradient (0–20 mS/cm in 200 ml) at pH 6.8. The final product was exchanged into PBS pH 7.2 by a HiPrep 26/10 desalting column (Amersham Biosciences).

The activity of BNP-HSA can be assayed using an in vitro NPR-A/cGMP Assay.

[1269] Natriuretic peptide receptor-A (NPR-A) is the signaling receptor for BNP, and as such, is responsible for most of BNP's biological effects. BNP bioactivity is mediated by NPR-A guanylyl cyclase domain that converts GTP to cGMP upon activation. A convenient assay for BNP activity is to measure the BNP stimulation of a 293F cell line that stably over-expresses NPR-A. The cGMP production in the cells after exposure to BNP can be measured by cGMP ELISA.

Method of Screening NPR-A 293F stable clones.

[1270] The open reading frame of human NPR-A was constructed into pcDNA3.1 expression vector (Invitrogen). 293F cells were stably transfected with the plasmid DNA by Lipofectamine method and selected by 0.8 μg/ml G418. 293F/NPR-A stable clones were screened for best response to recombinant BNP.

Measurement of cGMP activation.

[1271] cGMP activation by BNP was carried out in 293F/NPR-A cells and measured by CatchPoint cyclic-GMP fluorescent assay kit (Molecular Devices, Sunnyvale, CA, USA). Briefly, 50,000 cells/well of 293F/NPR-A cells cultured in a 96-well plate were washed into 80 μl prestimulation buffer (Krebs-Ringer Bicarbonate Buffer with 10 mM glucose, pH 7.4, 15 nM sodium bicarbonate, and 0.75 mM 3-isobutyl-1-methylxanthine). BNP-HSA or recombinant BNP in 40 µl prestimulation buffer was added to the cells at 37°C for 10 min. The cells were lysed with 40 µl Lysis Buffer for 10 min with shaking. The amounts of cGMP in the lysates were quantitated as per the manufacturer's instruction.

Result

[1272] The dose-response relationship of BNP-HSA and recombinant BNP were determined (see Figure 8). The maximal activities of Construct ID # 3691 and recombinant BNP were similar (1.63 ± 0.016 vs. 1.80 ± 0.016 pm, respectively), with EC50 values of 28.4 ± 1.2, and 0.46 ± 1.1 nM, respectively.

<u>*BNP-HSA decreases blood pressure in vivo.*</u>

Method

[1273] BNP reduces blood pressure by direct vasodilation as well as by suppression of renin/angiotensin/endothelin/aldosterone systems. The ability of BNP-HSA to decrease arterial blood pressure was tested in three-month old male spontaneously hypertensive rats purchased from Taconic (Germantown, NY, USA). Spontaneously hypertensive rats are genetically hypertensive with onset of high blood pressure after three months of age. BNP-HSA or recombinant BNP was reconstituted in 0.3 cc PBS per rat. The drugs were delivered via tail vein injection. Systolic and diastolic blood pressures were recorded by cuff-tail method using XBP-1000 System (Kent Scientific, Torrington, CT, USA). For each blood pressure data point, 4-5 consecutive readings were taken and averaged. Mean arterial pressure (MAP) was calculated as 1/3 systolic pressure + 2/3 diastolic pressure. For dose-response determination, blood pressures were measured 20 h after pC4:SPCON.BNP1-32/HSA administration at doses of 0.5, 2, 6, and 18 nmol/kg.

Result

[1274] The typical systolic pressure of spontaneously hypertensive rats was 180-200 mmHg before dosing. A single bolus of 6 nmol/kg BNP-HSA delivered via tail vein intravenous injection lowered both systolic and diastolic pressure, which accounted for more than 30 mmHg mean arterial pressure (MAP) reduction. The lowered blood pressure was steady and continued for a day and then gradually returned to the baseline over several days (see Figure 9). In contrast, due to its instantaneous clearance, a single 6 nmol/kg bolus of recombinant BNP, produced only a very transient MAP decrease of about ~15 mmHg.

[1275] In addition, the dose-response 20 hours post injection of a bolus of BNP-HSA was determined in four spontaneously hypertensive rats. 0.5 nmol/kg BNP-HSA had an average of 7 mmHg MAP reduction, while 6 nmol/kg BNP-HSA had an average of 30 mmHg MAP reduction, and a high dose of 18 nmol/kg BNP-HSA only lowered the blood pressure slightly more than 6 nmol/kg.

<u>*In vivo induction of plasma cGMP by BNP-HSA.*</u>

Method

[1276] The intracellular cGMP activation by BNP results in its release from the cell to circulation. The plasma cGMP level correlates with BNP-induced cardiovascular and renal physiology. Plasma cGMP has been used as a biomarker for *in vivo* BNP action. To test the induction of plasma cGMP by BNP-HSA *in vivo*, eleven- to 12-week-old male C57/BL6 mice received a single bolus of recombinant BNP or BNP-HSA at a 6 nmol/kg dose via tail vein. Plasma was prepared from the tail bleeds at 5, 10, 20, 40, and 80 min time points for the recombinant BNP dosing group and at additional 640, 1440, 2880, and 5760 min for the BNP-HSA group. Plasma samples from mice treated with PBS as the vehicle control were collected as the zero time points. cGMP levels were determined by CatchPoint cyclic-GMP fluorescent assay kit according to the manufacture's instruction.

Result

[1277] Following a single intravenous bolus of 6 nmol/kg recombinant BNP or BNP-HSA, peak plasma cGMP levels over the baseline were increased 3.9- or 5.6-fold, respectively (see Figure 10). In addition, the one-phase exponential decay half-life of cGMP following recombinant BNP treatment was 16 min (10 to 42 min, 95%CI), while the one-phase exponential decay half-life of cGMP following BNP-HSA administration was 1538 min (1017 to 3153 min, 95%CI).

<u>*In vivo Pharmacokinetic analysis of BNP albumin fusion encoded by construct ID* 3691.</u>

Method

[1278] Eleven- to 12-week-old male C57/BL6 mice (obtained from Ace Animals, Boyertown, PA, USA) weighed 25.1 ± 0.12 g at the time of the study. All animals were dosed at a volume of 10 ml/kg body weight. Predose animals were injected with PBS. Recombinant BNP was injected intravenously in the tail or subcutaneously in the mid-scapular region.

[1279] Pharmacokinetic analysis was performed on the following groups:

Table 8.

Group	Drug	Dose (mg/kg)	Route	N/time	Time (hours)
1	BNP-HSA	2.19	Subcutaneous	3	0.5, 2, 6, 16, 24, 32, 48, 72, 96
2	BNP-HSA	2.19	Intravenous	3	0.083, 2, 6, 16, 24, 32, 48, 72, 96
3	Vehicle	0	Subcutaneous	3	predose
4	Vehicle	0	Intravenous	3	predose

[1280] Blood was sampled from the inferior vena cava, placed into an EDTA-coated microtainer, and stored on ice. The samples were centrifuged in a microcentrifuge at 14,000 rpm (16,000 ×g) for 10 minutes at room temperature. The plasma was transferred into cluster tubes and stored at –80°C.

[1281] BNP-HSA concentrations in plasma samples were determined using BNP EIA Kit (Phoenix Pharmaceutical, Belmont, CA, USA). The standard curves were generated at the same time on the same plate with testing samples. The detection limit was 0.11 ng/mL for recombinant BNP. The assay detects recombinant BNP and does not cross react to mouse BNP.

[1282] Analysis was conducted by noncompartmental methods (WinNonlin; version 4.1; Pharsight Corp.,Mountain View, CA, USA). The mean plasma concentration at each time was used in the analysis. A linear up/log down trapezoidal method was used to calculate the $AUC0\text{-}_{t}$. Extrapolation to infinity $AUC_{0\text{-}\infty}$ was done by dividing the last observed concentration by the terminal elimination rate constant. Data were uniformly weighted for these analyses.

Result

[1283] The mean baseline concentration of BNP-HSA in plasma as detected in the pre-dose samples was approximately 0.081–0.095 µg/ml. Following a single intravenous or subcutaneous injection, BNP-HSA had terminal elimination half-lives of 11.2 (intravenous delivery) or 19.3 h (subcutaneous delivery), while the half-life of recombinant BNP in mice was 3.1 min. Non compartmental analysis of BNP-HSA revealed that BNP-HSA had the following characteristics:

Table 9.

	Unit	Intravenous	Subcutaneous
t_{max}	h	NA	16
C_{max}	µg/ml	NA	11.2
$t_{1/2,term}$	h	11.2	19.3
$AUC_{0\text{-}\infty}$	(h · µg/ml)/(mg/kg)	658.9	227.9
V_{ss}	ml/kg	37	NA
V_z or V_z/F	ml/kg	53.5	268
CL or CL/F	ml/h/kg	3.3	9.6
MRT	h	11.2	19.8
Bioavailability	%		34.6

C_{max}, peak plasma concentration of the drug; t_{max}, time of maximum plasma concentration; $AUC_{0\text{-}\infty}$, area under the plasma drug concentration-time curve from time 0 to infinite time; $t_{1/2,term}$, terminal elimination phase half-life; CL, clearance after intravenous dosing; CL/F, apparent clearance after subcutaneous dosing; V_{ss}, volume of distribution at steady-state after intravenous dosing; V_z: volume of distribution during the terminal phase after intravenous dosing; V_z/F, volume of distribution during the terminal phase after subcutaneous dosing; NA, not applicable.

[1284] Five points at the terminal phase of the intravenous profile and four points at the terminal phase of the subcutaneous profile were selected for the terminal half-life calculation. The resulting AUC during this terminal phase was approximately 10% of the total AUC for the intravenous and subcutaneous profiles, respectively. This is compared to only 2% and 4% of the total AUC for the intravenous and subcutaneous profile, respectively, when the last three points were selected for the terminal half-life calculation.

EXAMPLE 81: Construct ID # 3618, BNP(2X)-HSA, Generation.

[1285] Construct ID # 3618, pC4:SPCON.BNP1-32(2x)/HSA, comprises DNA encoding a BNP albumin fusion protein which has a consensus leader sequence, secreton, followed by two processed, active BNP peptides (amino acids 1-32) in tandem fused to the amino-terminus of the mature form of HSA in the mammalian expression vector pC4.

Cloning of BNP cDNA for construct 3618

[1286] The polynucleotide encoding the duplicate BNP moiety was first PCR amplified from the processed active form of BNP (amino acids 1-32) using four primers BNP-1, BNP-2, BNP-3, and BNP-4, described below, to create two fragments A and B. Following amplification, two purified fragments (A and B) were mixed in an equal molar amount and used as a PCR template and amplified with primers BNP-5 and BNP-6, as

described below. The BNP(2X) insert was then digested with *Bam*HI and *Cla*I and ligated into pC4HSA vector pre-digested with *Bam*HI and *Cla*I resulting in construct 3618. Construct ID # 3618 encodes an albumin fusion protein containing a consensus leader sequence, secrecon (SEQ ID No:111), and two, tandem copies of the processed, active form of BNP, followed by the mature HSA protein (see SEQ ID No:483 for construct 3618 in Table 2).

[1287] Four oligonucleotides suitable for PCR amplification of the polynucleotides encoding two fragments of BNP protein were first synthesized:

BNP-1 5'AGCCCCAAGATGGTGCAAGGGTCTGGCTGCTTTGGGAGGAAGATGGACCGGATCAGCTCCTCCAGTG GCTGGGCT GCAAAGTGCTGAGGCGGCAT-3' (SEQ ID NO:486)

BNP-2 5'-CCTTGCACCATCTTGGGGCTATGCCGCCTCAGCACTTTGC-3' (SEQ ID NO:487)

BNP-3 5'-GCAAAGTGCTGAGGCGGCATAGCCCCAAGATGGTGCAAGG-3' (SEQ ID NO:488)

BNP-4 5'-AGTCCCATCGATGAGCAACCTCACTCTTGTGTGCATCATGCCGCCTC AGCACTTTGC-3' (SEQ ID NO:489)

[1288] Using primer sets BNP-1/BNP-2 and BNP-3/BNP-4, two BNP proteins fragments (A and B, respectively) were PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template. Fragments A and B were purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)), mixed at equal molar amounts, and used as a template for PCR amplification using two additional oligonucleotides suitable for PCR amplification, BNP-5 and BNP-6:

BNP-5: 5'-GAGCGC<u>GGATCC</u>AAGCTTCCGCCATC*ATGTGGTGGCGCCTGTGGTGGCTGCTGCTGCTGCTGCTGCTGCT GTGGCCCATGGTGTGGGCC*AGCCCCAAGCTGGTGCAAGG -3' (SEQ ID NO:463)

BNP-6: 5'-AGTCCC<u>ATCGAT</u>GAGCAACCTCACTCTTGTGTGCATCATGCCGCCTCAGCACTTTGC-3' (SEQ ID NO:464)

[1289] BNP-5 incorporates a *Bam* HI cloning site (underlined), polynucleotides encoding a consensus leader sequence (SEQ ID No:111) (italicized), and polynucleotides encoding the first seven amino acid sequence of BNP (bolded). In BNP-6, the underlined sequence is a *Cla* I site, and the polynucleotides that follow it contains the reverse complement of DNA encoding the last 6 amino acids of BNP (bolded) and the first 10 amino acids of the mature HSA protein. Using these two primers, a consensus leader sequence and two tandem copies of active BNP peptides were PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

[1290] The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bam* HI and *Cla* I. After further purification of the *Bam* HI-*Cla* I fragment by gel electrophoresis, the product was cloned into *Bam* HI /*Cla* I digested pC4:HSA to produce construct ID # 3618. The expression construct was sequence verified.

<u>Expression and Purification of Construct ID # 3618.</u>

Expression in 293F cells.

[1291] Construct ID # 3618, pC4:SPCON.BNP1-32(2x)/HSA, was transfected into 293F cells by methods known in the art (see Example 6).

Purification from 293F cell supernatant.

[1292] pC4:SPCON.BNP1-32(2x)/HSA encoded by Construct ID # 3618 was purified as previously described above in Example 80 under subsection heading "Purification from 203F cell supernatant."

<u>The Activity of BNP(2X)-HSA can be assayed using an In Vitro NPR-A/cGMP Assay.</u>

[1293] The activity of BNP(2X)-HSA encoded by Construct ID # 3618 can be assayed *in vitro* using an NPR-A/cGMP assay as previously described in Example 80 under subsection heading, "The activity of BNP-HSA can be assayed using an in vitro NPR-A/cGMP Assay," and "Method of Screening NPR-A 203F Stable Clones."

Result

[1294] The dose-response relationship of BNP(2X)-HSA and recombinant BNP were determined (see Figure 8). The maximal activities of BNP(2X)-HSA encoded by Construct ID # 3618, and recombinant BNP were similar (1.68 ± 0.021, vs. 1.80 ± 0.016 pm, respectively), with EC50 values of 9.8 ± 1.1, and 0.46 ± 1.1 nM respectively.

[1295] The entire disclosure of each document cited (including patents, patent applications, patent publications, journal articles, abstracts, laboratory manuals, books, or other disclosures) as well as information available through identifiers specific to databases such as GenBank, GeneSeq, or the CAS Registry, referred to in this application are herein incorporated by reference in their entirety.

[1296] Furthermore, the specification and sequence listing of each of the following U.S. applications are herein incorporated by reference in their entirety: U.S. Application No. 60/542,274, filed February 4, 2005; U.S. Application No. 60/549,901, filed March 5, 2004; U.S. Application No. 60/556,906, filed March 29, 2004; and U.S. Application No. 60/636,603, filed December 17, 2004.

Applicant's File Reference Number: PF612PCT	International Application Number: Unassigned

INDICATIONS RELATING TO DEPOSITED BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited biological material referred to in Table 3, page 25 of the description.

B. IDENTIFICATION OF DEPOSIT:

Further deposits are identified on an additional sheet: ☐

Name of Depository: **American Type Culture Collection**
Address of Depository: **10801 University Boulevard**
Manassas, Virginia 20110-2209
United States of America

	Accession Number	Date of Deposit		Accession Number	Date of Deposit
1	PTA-3759	04-Oct-2001	2	PTA-3764	04-Oct-2001
3	PTA-3941	19-Dec-2001	4	PTA-3763	04-Oct-2001
5	PTA-3940	19-Dec-2001	6	PTA-3942	19-Dec-2001
7	PTA-3939	19-Dec-2001	8	PTA-3943	19-Dec-2001
9	PTA-4670	16-Sep-2002	10		

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

What is claimed:

1. An albumin fusion protein comprising a member selected from the group consisting of:

(a) a Therapeutic protein:X and albumin comprising the amino acid sequence of SEQ ID NO:1;

(b) a Therapeutic protein:X and a fragment or a variant of the amino acid sequence of SEQ ID NO:1, wherein said fragment or variant has albumin activity;

(c) a Therapeutic protein:X and a fragment or a variant of the amino acid sequence of SEQ ID NO:1, wherein said fragment or variant has albumin activity, and further wherein said albumin activity is the ability to prolong the shelf life of the Therapeutic protein:X compared to the shelf-life of the Therapeutic protein:X in an unfused state;

(d) a Therapeutic protein:X and a fragment or a variant of the amino acid sequence of SEQ ID NO:1, wherein said fragment or variant has albumin activity, and further wherein the fragment or variant comprises the amino acid sequence of amino acids 1-387 of SEQ ID NO:1;

(e) a fragment or variant of a Therapeutic protein:X and albumin comprising the amino acid sequence of SEQ ID NO:1, wherein said fragment or variant has a biological activity of the Therapeutic protein:X;

(f) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (e), wherein the Therapeutic protein:X, or fragment or variant thereof, is fused to the N-terminus of albumin, or the N-terminus of the fragment or variant of albumin;

(g) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (e), wherein the Therapeutic protein:X, or fragment or variant thereof, is fused to the C-terminus of albumin, or the C-terminus of the fragment or variant of albumin;

(h) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (e), wherein the Therapeutic protein:X, or fragment or variant thereof, is fused to the N- terminus and C-terminus of albumin, or the N-terminus and the C-terminus of the fragment or variant of albumin;

(i) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (e), which comprises a first Therapeutic protein:X, or fragment or variant thereof, and a second Therapeutic protein:X, or fragment or variant thereof, wherein said first Therapeutic protein:X, or fragment or variant thereof, is different from said second Therapeutic protein:X, or fragment or variant thereof;

(j) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (i), wherein the Therapeutic protein:X, or fragment or variant thereof, is separated from the albumin or the fragment or variant of albumin by a linker; and

(k) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (j), wherein the albumin fusion protein has the following formula:

R1-L-R2; R2-L-R1; or R1-L-R2-L-R1,

and further wherein R1 is Therapeutic protein:X, or fragment or variant thereof, L is a peptide linker, and R2 is albumin comprising the amino acid sequence of SEQ ID NO:1 or a fragment or variant of albumin.

2. The albumin fusion protein of claim 1, wherein the shelf-life or plasma stability of the albumin fusion protein is greater than the shelf-life or plasma stability of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

3. The albumin fusion protein of claim 1, wherein the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin, or fragment or variant thereof, is greater than the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

4. The albumin fusion protein of claim 1, wherein the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin, or fragment or variant thereof, is greater than the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

5. An albumin fusion protein comprising a Therapeutic protein:X, or fragment or variant thereof, inserted into an albumin, or fragment or variant thereof, comprising the amino acid sequence of SEQ ID NO:1 or fragment or variant thereof.

6. An albumin fusion protein comprising a Therapeutic protein:X, or fragment or variant thereof, inserted into an albumin, or

fragment or variant thereof, comprising an amino acid sequence selected from the group consisting of:

(a) amino acids 54 to 61 of SEQ ID NO:1;

(b) amino acids 76 to 89 of SEQ ID NO:1;

(c) amino acids 92 to100 of SEQ ID NO:1;

(d) amino acids 170 to 176 of SEQ ID NO:1;

(e) amino acids 247 to 252 of SEQ ID NO:1;

(f) amino acids 266 to 277 of SEQ ID NO:1;

(g) amino acids 280 to 288 of SEQ ID NO:1;

(h) amino acids 362 to 368 of SEQ ID NO:1;

(i) amino acids 439 to 447 of SEQ ID NO:1;

(j) amino acids 462 to 475 of SEQ ID NO:1;

(k) amino acids 478 to 486 of SEQ ID NO:1; and

(l) amino acids 560 to 566 of SEQ ID NO:1.

7. The albumin fusion protein of claim 5, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the shelf-life or plasma stability of the Therapeutic protein:X, or fragment or variant thereof, as compared to the shelf-life or plasma stability of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

8. The albumin fusion protein of claim 6, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the shelf-life or plasma stability of the Therapeutic protein:X, or fragment or variant thereof, as compared to the shelf-life or plasma stability of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

9. The albumin fusion protein of claim 5, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin as compared to the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

10. The albumin fusion protein of claim 6, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin as compared to the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

11. The albumin fusion protein of claim 5 wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin compared to the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

12. The albumin fusion protein of claim 6 wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin compared to the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

13. The albumin fusion protein of any one of claims 1-12, which is non-glycosylated.

14. The albumin fusion protein of any one of claims 1-12, which is expressed in yeast.

15. The albumin fusion protein of claim 14, wherein the yeast is glycosylation deficient.

16. The albumin fusion protein of claim 14 wherein the yeast is glycosylation and protease deficient.

17. The albumin fusion protein of any one of claims 1-12, which is expressed by a mammalian cell.

18. The albumin fusion protein of any one of claims 1-12, wherein the albumin fusion protein is expressed by a mammalian cell in culture.

19. The albumin fusion protein of any one of claims 1-12, wherein the albumin fusion protein further comprises a secretion leader sequence.

20. A composition comprising the albumin fusion protein of any one of claims 1-12 and a pharmaceutically acceptable carrier.

21. A kit comprising the composition of claim 20.

22. A method of treating a disease or disorder in a patient, comprising the step of administering the albumin fusion protein of any one of claims 1-12.

23. The method of claim 22, wherein the disease or disorder comprises indication:Y.

24. A method of treating a patient with a disease or disorder that is modulated by Therapeutic protein:X, or fragment or variant thereof, comprising the step of administering an effective amount of the albumin fusion protein of any one of claims 1-12.

25. The method of claim 24, wherein the disease or disorder is indication:Y.

26. A method of extending the shelf life or plasma stability of Therapeutic protein:X, or fragment or variant thereof, comprising the step of fusing the Therapeutic protein:X, or fragment or variant thereof, to albumin, or fragment or variant thereof, sufficient to extend the shelf-life or plasma stability of the Therapeutic protein:X, or fragment or variant thereof, compared to the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

27. A nucleic acid molecule comprising a polynucleotide sequence encoding the albumin fusion protein of any one of claims 1-12.

28. A vector comprising the nucleic acid molecule of claim 27.

29. A host cell comprising the nucleic acid molecule of claim 28.

```
  1 GAT GCA CAC AAG AGT GAG GTT GCT CAT CGG TTT AAA GAT TTG GGA GAA GAA AAT TTC AAA 60
  1 D   A   H   K   S   E   V   A   H   R   F   K   D   L   G   E   E   N   F   K   20

 61 GCC TTG GTG TTG ATT GCC TTT GCT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120
 21 A   L   V   L   I   A   F   A   Q   Y   L   Q   Q   C   P   F   E   D   H   V   40

121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GCA AAA ACA TGT GTT GCT GAT GAG TCA GCT GAA 180
 41 K   L   V   N   E   V   T   E   F   A   K   T   C   V   A   D   E   S   A   E   60

181 AAT TGT GAC AAA TCA CTT CAT ACC CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 240
 61 N   C   D   K   S   L   H   T   L   F   G   D   K   L   C   T   V   A   T   L   80

241 CGT GAA ACC TAT GGT GAA ATG GCT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300
 81 R   E   T   Y   G   E   M   A   D   C   C   A   K   Q   E   P   E   R   N   E   100

301 TGC TTC TTG CAA CAC AAA GAT GAC AAC CCA AAC CTC CCC CGA TTG GTG AGA CCA GAG GTT 360
101 C   F   L   Q   H   K   D   D   N   P   N   L   P   R   L   V   R   P   E   V   120

361 GAT GTG ATG TGC ACT GCT TTT CAT GAC AAT GAA GAG ACA TTT TTG AAA AAA TAC TTA TAT 420
121 D   V   M   C   T   A   F   H   D   N   E   E   T   F   L   K   K   Y   L   Y   140

421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTC TTT GCT AAA AGG 480
141 E   I   A   R   R   H   P   Y   F   Y   A   P   E   L   L   F   F   A   K   R   160
```

Figure 1A

```
481 TAT AAA GCT GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCT GCC TGC CTG TTG CCA 540
161 Y   K   A   A   F   T   E   C   C   Q   A   A   D   K   A   A   C   L   L   P   180

541 AAG CTC GAT GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC AAA CAG AGA CTC AAA TGT 600
181 K   L   D   E   L   R   D   E   G   K   A   S   S   A   K   Q   R   L   K   C   200

601 GCC AGT CTC CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG GCT CGC CTG AGC 660
201 A   S   L   Q   K   F   G   E   R   A   F   K   A   W   A   V   A   R   L   S   220

661 CAG AGA TTT CCC AAA GCT GAG TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720
221 Q   R   F   P   K   A   E   F   A   E   V   S   K   L   V   T   D   L   T   K   240

721 GTC CAC ACG GAA TGC TGC CAT GGA GAT CTG CTT GAA TGT GCT GAT GAC AGG GCG GAC CTT 780
241 V   H   T   E   C   C   H   G   D   L   L   E   C   A   D   D   R   A   D   L   260

781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA 840
261 A   K   Y   I   C   E   N   Q   D   S   I   S   S   K   L   K   E   C   C   E   280

841 AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT GAG ATG CCT GCT 900
281 K   P   L   L   E   K   S   H   C   I   A   E   V   E   N   D   E   M   P   A   300

901 GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC AAA AAC TAT GCT 960
301 D   L   P   S   L   A   A   D   F   V   E   S   K   D   V   C   K   N   Y   A   320
```

Figure 1B

```
 961 GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT 1020
 321 E   A   K   D   V   F   L   G   M   F   L   Y   E   Y   A   R   R   H   P   D   340

1021 TAC TCT GTC GTG CTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 1080
 341 Y   S   V   V   L   L   L   R   L   A   K   T   Y   E   T   T   L   E   K   C   360

1081 TGT GCC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 1140
 361 C   A   A   A   D   P   H   E   C   Y   A   K   V   F   D   E   F   K   P   L   380

1141 GTG GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG 1200
 381 V   E   E   P   Q   N   L   I   K   Q   N   C   E   L   F   E   Q   L   G   E   400

1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 1260
 401 Y   K   F   Q   N   A   L   L   V   R   Y   T   K   K   V   P   Q   V   S   T   420

1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320
 421 P   T   L   V   E   V   S   R   N   L   G   K   V   G   S   K   C   C   K   H   440

1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC CTG AAC CAG TTA 1380
 441 P   E   A   K   R   M   P   C   A   E   D   Y   L   S   V   V   L   N   Q   L   460

1381 TGT GTG TTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440
 461 C   V   L   H   E   K   T   P   V   S   D   R   V   T   K   C   C   T   E   S   480
```

Figure 1C

```
1441 TTG GTG AAC AGG CGA CCA TGC TTT TCA GCT CTG GAA GTC GAT GAA ACA TAC GTT CCC AAA 1500
 481 L   V   N   R   R   P   C   F   S   A   L   E   V   D   E   T   Y   V   P   K   500

1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GCA GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560
 501 E   F   N   A   E   T   F   T   F   H   A   D   I   C   T   L   S   E   K   E   520

1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620
 521 R   Q   I   K   K   Q   T   A   L   V   E   L   V   K   H   K   P   K   A   T   540

1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG AAG TGC TGC AAG 1680
 541 K   E   Q   L   K   A   V   M   D   D   F   A   A   F   V   E   K   C   C   K   560

1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 1740
 561 A   D   D   K   E   T   C   F   A   E   E   G   K   K   L   V   A   A   S   Q   580

1741 GCT GCC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782
 581 A   A   L   G   L   *                                  585
```

Figure 1D

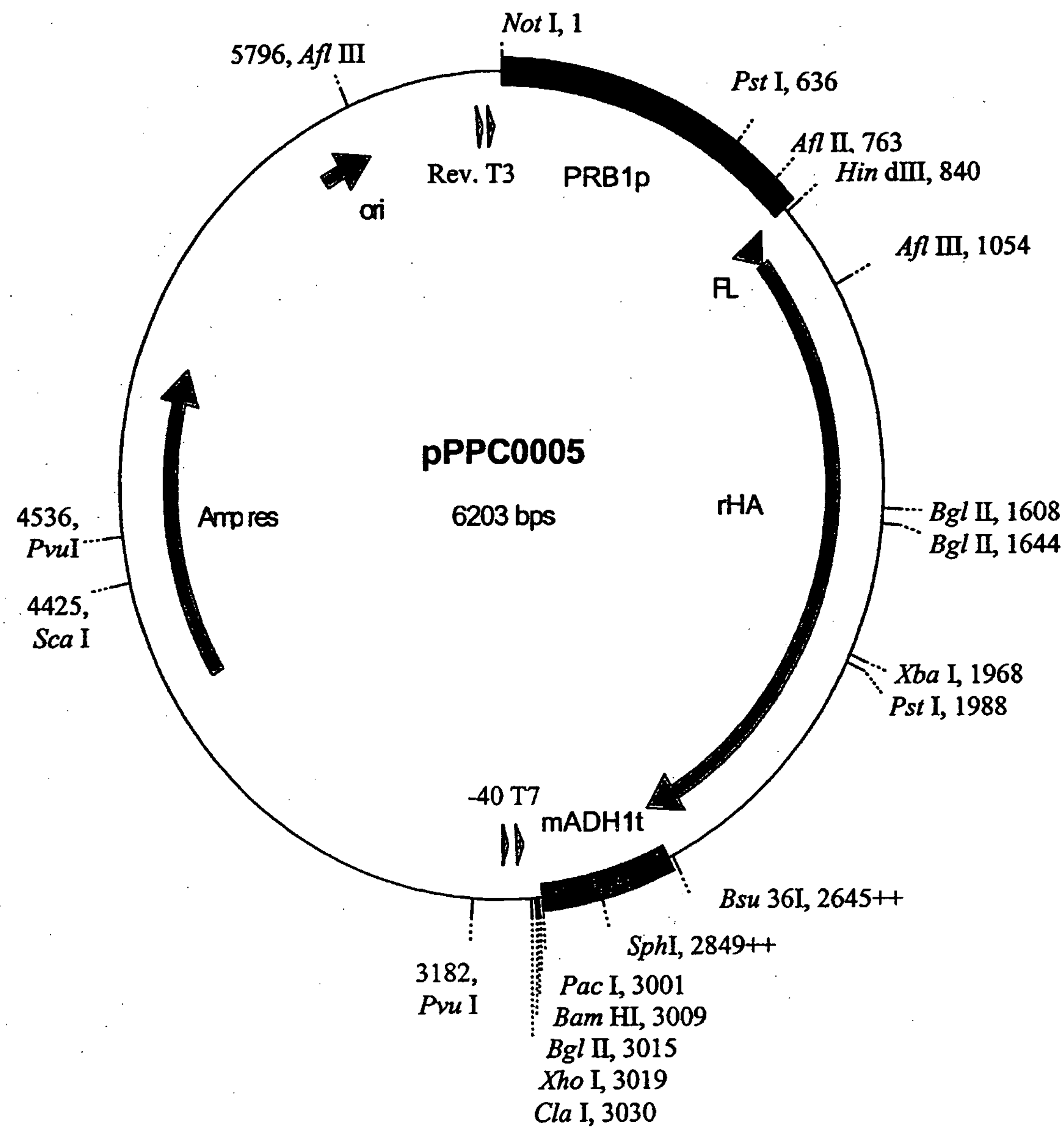

Not I, 1
5796, Afl III
Pst I, 636
Afl II, 763
Hin dIII, 840
Rev. T3
PRB1p
ori
Afl III, 1054
FL
pPPC0005
6203 bps
rHA
Amp res
4536,
PvuI
4425,
Sca I
Bgl II, 1608
Bgl II, 1644
Xba I, 1968
Pst I, 1988
-40 T7
mADH1t
Bsu 36I, 2645++
SphI, 2849++
3182,
Pvu I
Pac I, 3001
Bam HI, 3009
Bgl II, 3015
Xho I, 3019
Cla I, 3030

Figure 2

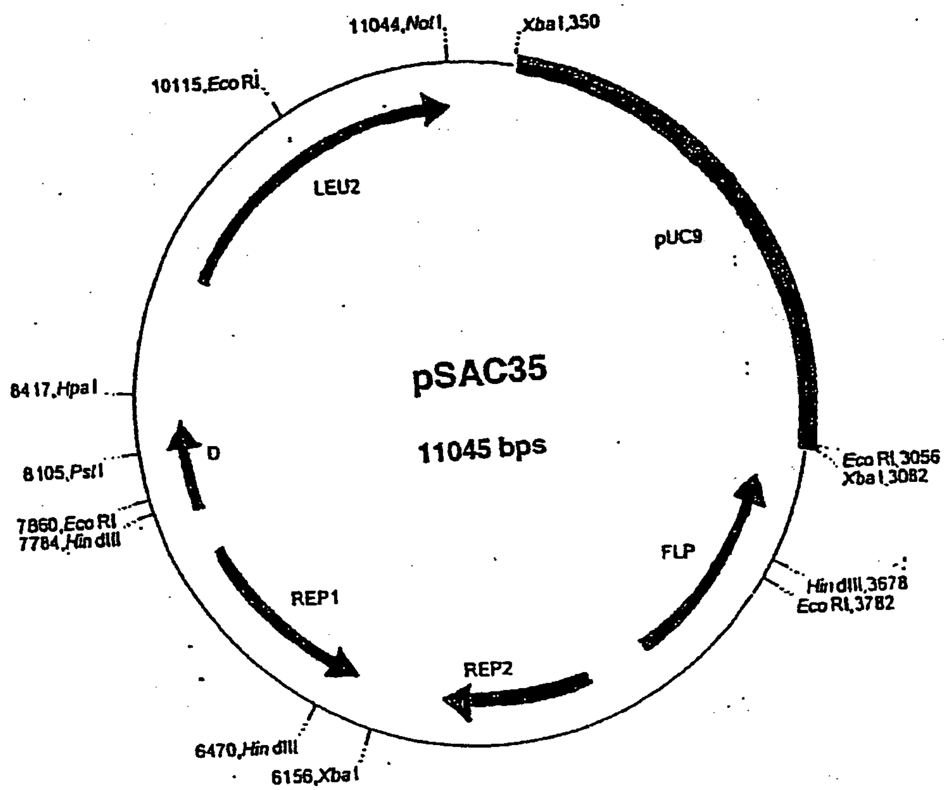
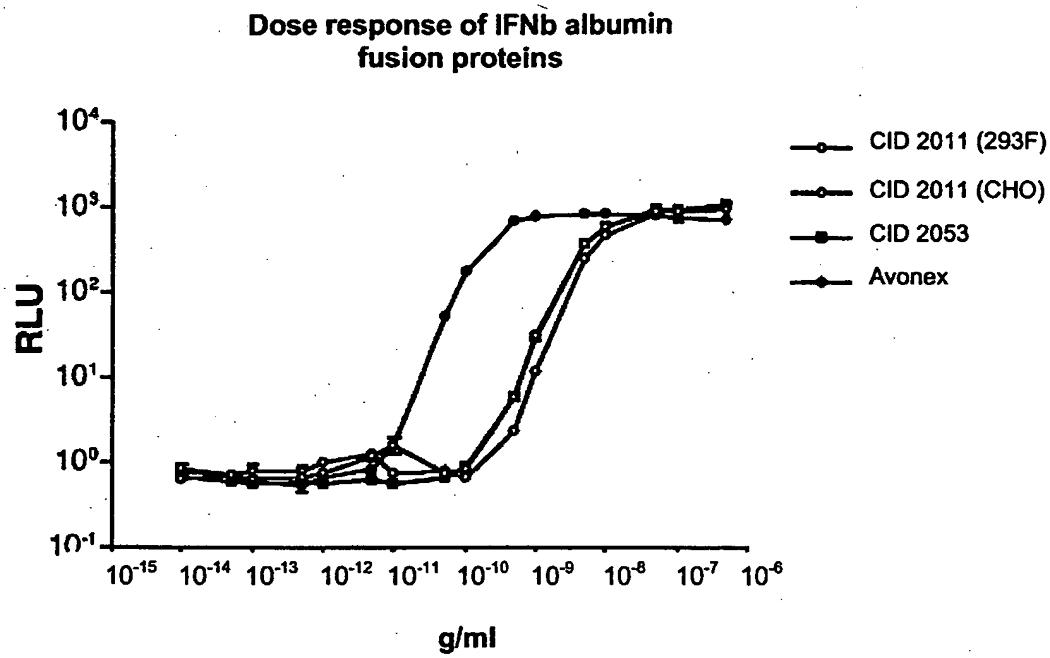

11044,NotI
XbaI,350
10115,EcoRI
LEU2
pUC9
pSAC35
11045 bps
8417,HpaI
8105,PstI
D
7860,EcoRI
7784,HindIII
EcoRI,3056
XbaI,3082
FLP
REP1
HindIII,3678
EcoRI,3782
REP2
6470,HindIII
6156,XbaI

Figure 3



Dose response of IFNb albumin fusion proteins
RLU
10^{4}
10^{3}
10^{2}
10^{1}
10^{0}
10^{-1}
10^{-15} 10^{-14} 10^{-13} 10^{-12} 10^{-11} 10^{-10} 10^{-9} 10^{-8} 10^{-7} 10^{-6}
g/ml
CID 2011 (293F)
CID 2011 (CHO)
CID 2053
Avonex

Figure 4

Inhibition of proliferation of HS294T melanoma cells by IFNa albumin fusion protein

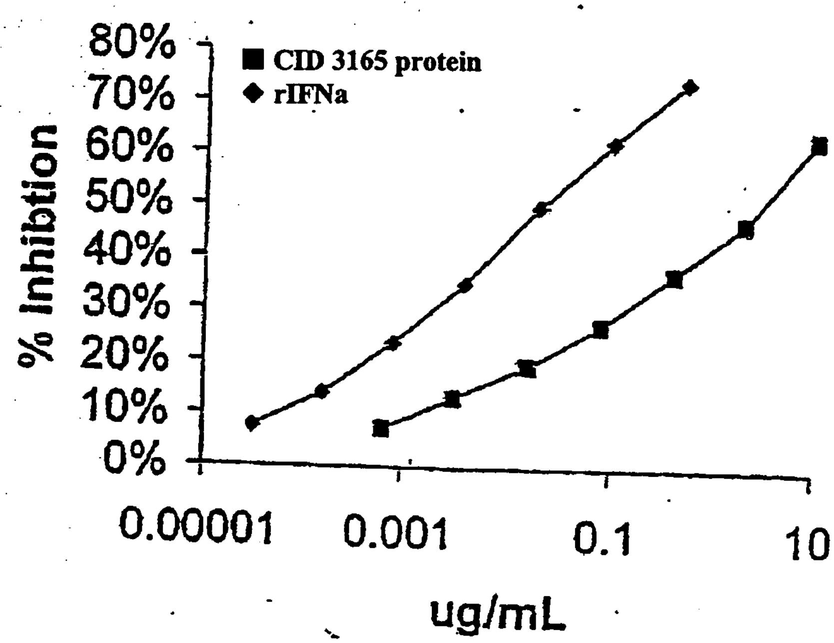


Figure 5

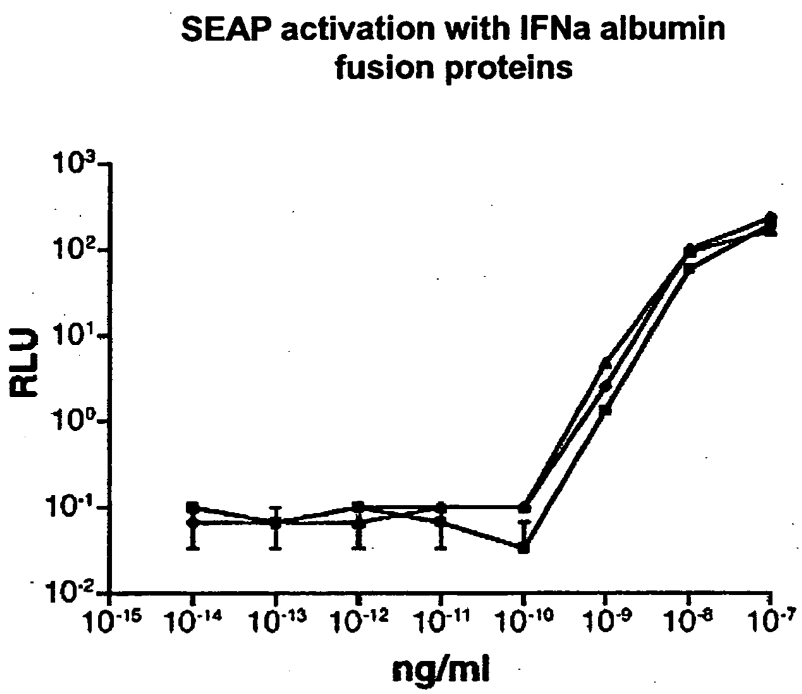

SEAP activation with IFNa albumin fusion proteins
RLU
10³
10²
10¹
10⁰
10⁻¹
10⁻²
10⁻¹⁵
10⁻¹⁴
10⁻¹³
10⁻¹²
10⁻¹¹
10⁻¹⁰
10⁻⁹
10⁻⁸
10⁻⁷
ng/ml

Figure 6

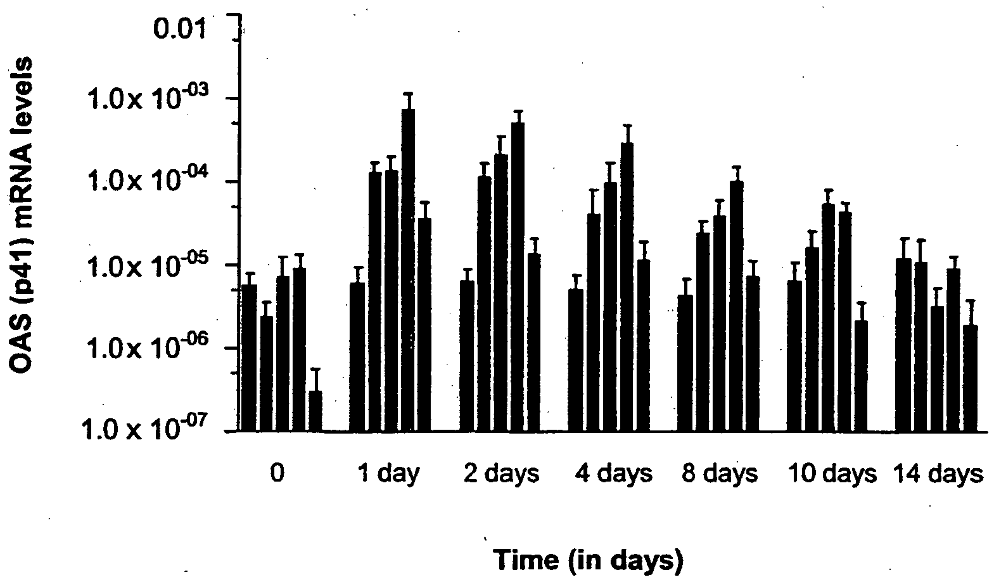

0.01
1.0x 10-03
1.0x 10-04
1.0x 10-05
1.0x 10-06
1.0 x 10-07
OAS (p41) mRNA levels
0
1 day
2 days
4 days
8 days
10 days
14 days
Time (in days)

Figure 7

Dose-response of recombinant BNP and BNP Albumin Fusion Proteins — BNP-HSA and BNP(2X)-HSA

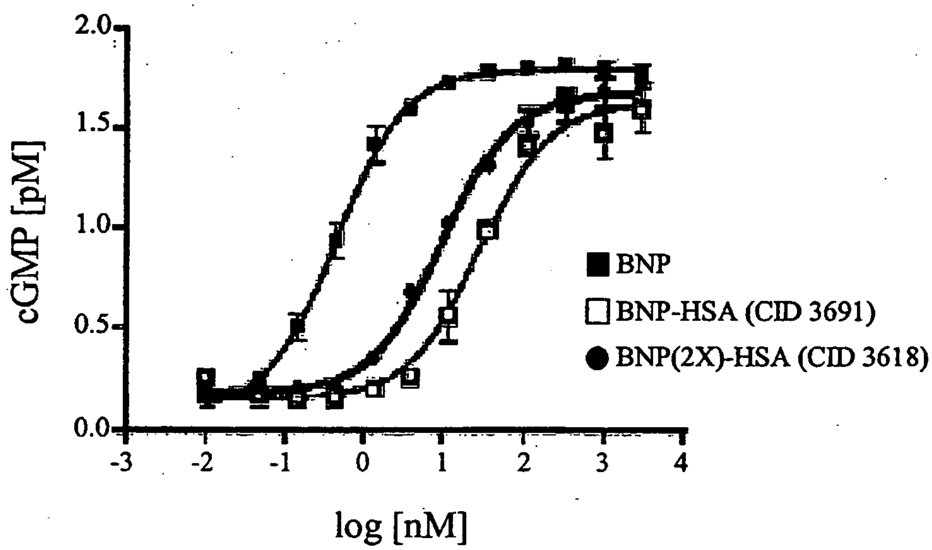


Figure 8

Effect of BNP Albumin Fusion Proteins
on Mean Arterial Pressure in
Spontaneously Hypertensive Rats

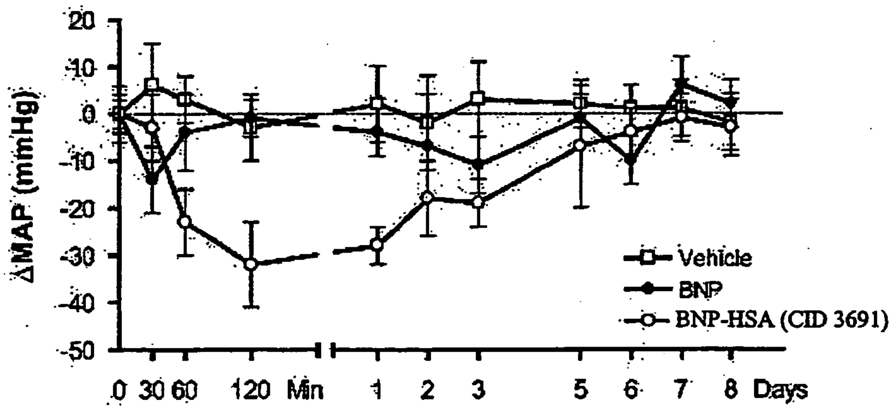


Figure 9

In Vivo cGMP Levels in Mice After an Intravenous Injection of Recombinant BNP or BNP Albumin Fusion Proteins

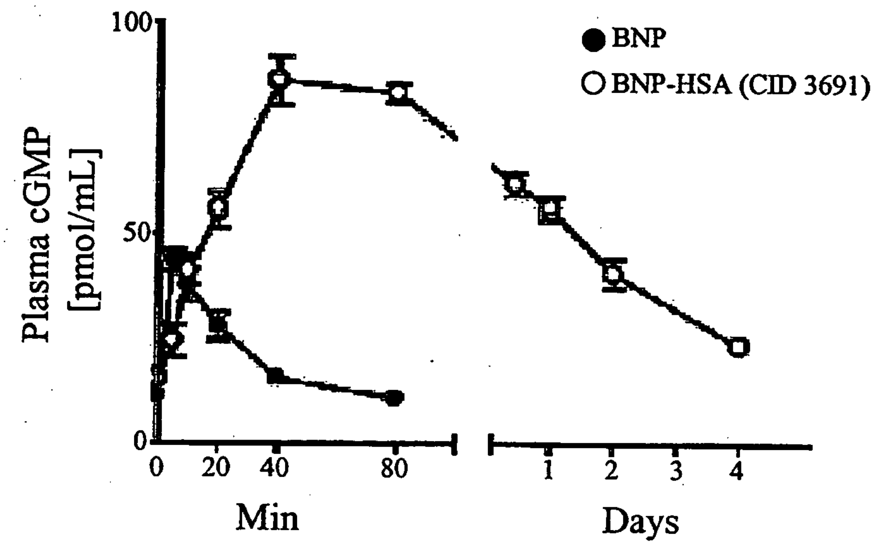
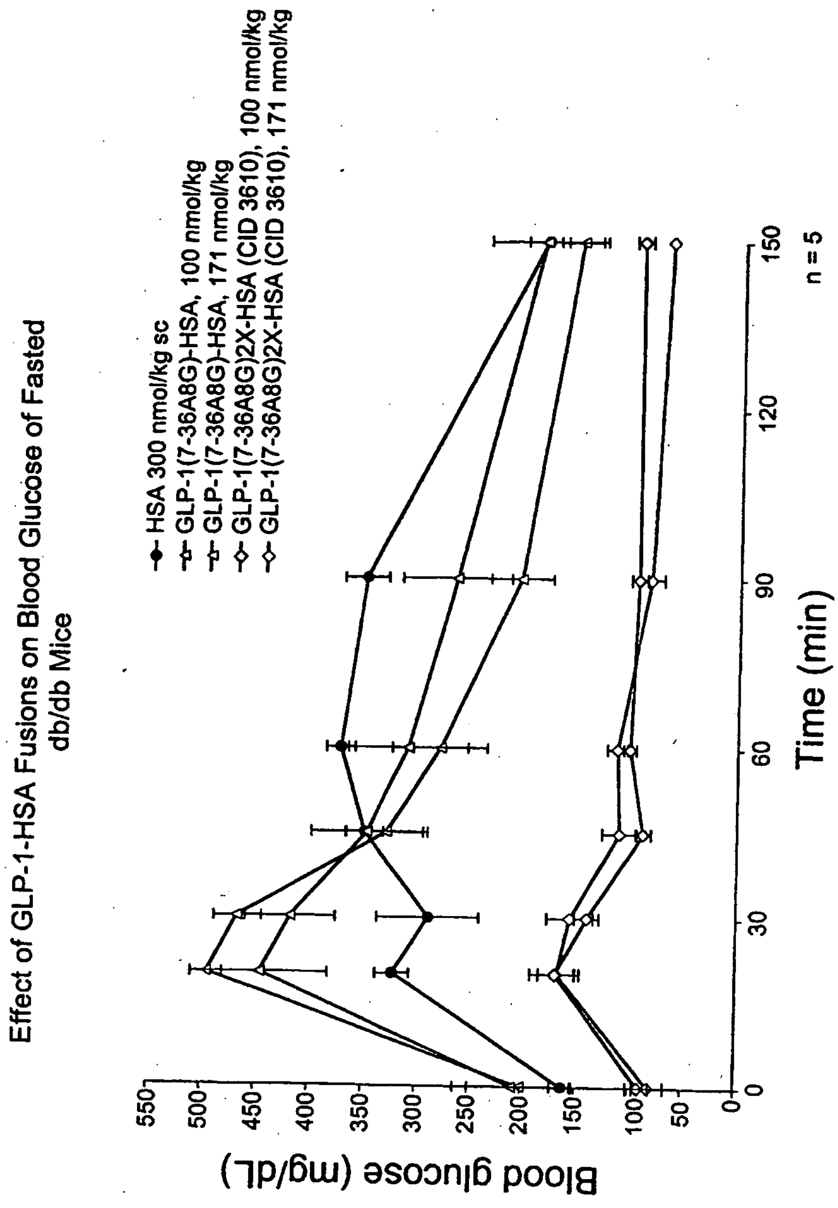


Figure 10



Effect of GLP-1-HSA Fusions on Blood Glucose of Fasted db/db Mice
HSA 300 nmol/kg sc
GLP-1(7-36A8G)-HSA, 100 nmol/kg
GLP-1(7-36A8G)-HSA, 171 nmol/kg
GLP-1(7-36A8G)2X-HSA (CID 3610), 100 nmol/kg
GLP-1(7-36A8G)2X-HSA (CID 3610), 171 nmol/kg
Blood glucose (mg/dL)
0
50
100
150
200
250
300
350
400
450
500
550
0
30
60
90
120
150
Time (min)
n = 5

Figure 11

<110> Human Genome Sciences, Inc.

<120> Albumin Fusion Proteins

<130> PF612PCT

<150> 60/542,274
<151> 2004-02-09

<150> 60/549,901
<151> 2004-03-05

<150> 60/556,906
<151> 2004-03-29

<150> 60/636,603
<151> 2004-12-17

<160> 489

<170> PatentIn Ver. 2.0

<210> 1
<211> 585
<212> PRT
<213> Homo sapiens

<400> 1
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp

500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 2
<211> 1782
<212> DNA
<213> Homo sapiens

<400> 2
gatgcacaca agagtgaggt tgctcatcgg tttaaagatt tgggagaaga aaatttcaaa 60
gccttggtgt tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta 120
aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180
aattgtgaca aatcacttca taccctttttt ggagacaaat tatgcacagt tgcaactctt 240
cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300
tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360
gatgtgatgt gcactgcttt tcatgacaat gaagagacat tttgaaaaa atacttatat 420
gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480
tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540
aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaaatgt 600
gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtggc tcgcctgagc 660
cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720
gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780
gccaagtata tctgtgaaaa tcaggattcg atctccagta aactgaagga atgctgtgaa 840
aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900
gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960
gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020
tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080
tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140
gtggaagagc ctcagaattt aatcaaacaa aactgtgagc tttttgagca gcttggagag 1200
tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260
ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320
cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380
tgtgtgttgc atgagaaaac gccagtaagt gacagagtca caaaatgctg cacagagtcc 1440
ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500
gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560
agacaaatca agaaacaaac tgcacttgtt gagcttgtga aacacaagcc caaggcaaca 1620
aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680
gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc tgcaagtcaa 1740
gctgccttag gcttataaca tctacattta aaagcatctc ag 1782

<210> 3
<211> 609
<212> PRT
<213> Homo sapiens

<400> 3

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20   25   30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35   40   45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50   55   60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65   70   75   80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85   90   95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100   105   110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115   120   125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130   135   140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145   150   155   160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165   170   175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180   185   190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195   200   205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210   215   220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225   230   235   240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245   250   255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260   265   270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275   280   285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290   295   300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305   310   315   320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser

```
            325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu


<210> 4
<211> 15
<212> PRT
<213> Artificial Sequence
```

<220>
<221> turn
<223> Linker peptide that may be used to join VH
and VL domains in an scFv.

<400> 4
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 5
<211> 394
<212> DNA
<213> Homo sapiens

<400> 5
gcggccgccg gatgcaaggg ttcgaatccc ttagctctca ttattttttg ctttttctct 60
tgaggtcaca tgatcgcaaa atggcaaatg gcacgtgaag ctgtcgatat tggggaactg 120
tggtggttgg caaatgacta attaagttag tcaaggcgcc atcctcatga aaactgtgta 180
acataataac cgaagtgtcg aaaaggtggc accttgtcca attgaacacg ctcgatgaaa 240
aaaataagat atatataagg ttaagtaaag cgtctgttag aaaggaagtt tttccttttt 300
cttgctctct tgtcttttca tctactattt ccttcgtgta atacagggtc gtcagataca 360
tagatacaat tctattaccc ccatccatac aatg 394

<210> 6
<211> 21
<212> PRT
<213> Homo sapiens

<400> 6
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala
20

<210> 7
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Stanniocalcin signal peptide

<400> 7
Met Leu Gln Asn Ser Ala Val Leu Leu Leu Leu Val Ile Ser Ala Ser
1 5 10 15

Ala

<210> 8
<211> 24
<212> PRT
<213> Homo sapiens

<400> 8
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

```
Tyr Ser Arg Gly Val Phe Arg Arg
            20

<210> 9
<211> 18
<212> PRT
<213> Homo sapiens

<400> 9
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser


<210> 10
<211> 18
<212> PRT
<213> Homo sapiens

<400> 10
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser


<210> 11
<211> 19
<212> PRT
<213> Homo sapiens

<400> 11
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1               5                   10                  15

Ile Ser Ala


<210> 12
<211> 86
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (84)
<223> Xaa equals any one of Glu or Asp

<400> 12
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Ala Phe Ala Ala Ser
1               5                   10                  15

Ser Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala
            20                  25                  30

Gln Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp
        35                  40                  45

Phe Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu
```

50 55 60

Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly
65 70 75 80

Val Ser Leu Xaa Lys Arg
85

<210> 13
<211> 24
<212> PRT
<213> Homo sapiens

<400> 13
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Glu Lys Arg
20

<210> 14
<211> 24
<212> PRT
<213> Homo sapiens

<400> 14
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg
20

<210> 15
<211> 21
<212> PRT
<213> Homo sapiens

<400> 15
Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1 5 10 15

Ser Leu Asp Lys Arg
20

<210> 16
<211> 19
<212> PRT
<213> Homo sapiens

<400> 16
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser

<210> 17
<211> 29
<212> PRT
<213> Homo sapiens

<400> 17
Met Glu Arg Ala Ala Pro Ser Arg Arg Val Pro Leu Pro Leu Leu Leu
1 5 10 15

Leu Gly Gly Leu Ala Leu Leu Ala Ala Gly Val Asp Ala
20 25

<210> 18
<211> 22
<212> PRT
<213> Homo sapiens

<400> 18
Met Met Lys Thr Leu Leu Leu Phe Val Gly Leu Leu Leu Thr Trp Glu
1 5 10 15

Ser Gly Gln Val Leu Gly
20

<210> 19
<211> 21
<212> PRT
<213> Homo sapiens

<400> 19
Met Leu Pro Leu Cys Leu Val Ala Ala Leu Leu Leu Ala Ala Gly Pro
1 5 10 15

Gly Pro Ser Leu Gly
20

<210> 20
<211> 24
<212> PRT
<213> Homo sapiens

<400> 20
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg
20

<210> 21
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 21
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ala Gly Val
1 5 10 15

Leu Gly

<210> 22
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 22
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Gly Val
1 5 10 15

Leu Gly

<210> 23
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 23
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
1 5 10 15

Leu Gly

<210> 24
<211> 18
<212> PRT
<213> Homo sapiens

<400> 24
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ala Gly Val
1 5 10 15

Ser Gly

<210> 25
<211> 18
<212> PRT
<213> Homo sapiens

<400> 25
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
1 5 10 15

Ser Gly

<210> 26
<211> 18

<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 26
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ala Gly Val
1 5 10 15

Ser Gly

<210> 27
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 27
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Gly Val
1 5 10 15

Ser Gly

<210> 28
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 28
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
1 5 10 15

Ser Gly

<210> 29
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (23)
<223> Variant of HSA native leader

<400> 29
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val

```
 1               5                   10                  15

Leu Gly Asp Leu His Lys Ser
            20

<210> 30
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic signal peptide

<400> 30
Met Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala Leu
 1               5                   10                  15

Trp Ala Pro Ala Arg Gly
            20

<210> 31
<211> 17
<212> PRT
<213> Homo sapiens

<400> 31
Met Phe Lys Ser Val Val Tyr Ser Ile Leu Ala Ala Ser Leu Ala Asn
 1               5                   10                  15

Ala

<210> 32
<211> 29
<212> PRT
<213> Homo sapiens

<400> 32
Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
 1               5                   10                  15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg
            20                  25

<210> 33
<211> 23
<212> PRT
<213> Homo sapiens

<400> 33
Met Lys Leu Ala Tyr Ser Leu Leu Leu Pro Leu Ala Gly Val Ser Ala
 1               5                   10                  15

Ser Val Ile Asn Tyr Lys Arg
            20

<210> 34
<211> 65
<212> PRT
<213> Homo sapiens

<400> 34
```

Met Lys Leu Lys Thr Val Arg Ser Ala Val Leu Ser Ser Leu Phe Ala
1   5   10   15

Ser Gln Val Leu Gly Gln Pro Ile Asp Asp Thr Glu Ser Gln Thr Thr
            20   25   30

Ser Val Asn Leu Met Ala Asp Asp Thr Glu Ser Ala Phe Ala Thr Gln
        35   40   45

Thr Asn Ser Gly Gly Leu Asp Val Val Gly Leu Ile Ser Met Ala Lys
    50   55   60

Arg
65

<210> 35
<211> 70
<212> PRT
<213> Homo sapiens

<400> 35
Met Lys Leu Lys Thr Val Arg Ser Ala Val Leu Ser Ser Leu Phe Ala
1   5   10   15

Ser Gln Val Leu Gly Gln Pro Ile Asp Asp Thr Glu Ser Gln Thr Thr
            20   25   30

Ser Val Asn Leu Met Ala Asp Asp Thr Glu Ser Ala Phe Ala Thr Gln
        35   40   45

Thr Asn Ser Gly Gly Leu Asp Val Val Gly Leu Ile Ser Met Ala Glu
    50   55   60

Glu Gly Glu Pro Lys Arg
65   70

<210> 36
<211> 58
<212> DNA
<213> Artificial Sequence

<220>
<223> primer used to generate XhoI and ClaI
site in pPPC0006

<400> 36
gcctcgagaa aagagatgca cacaagagtg aggttgctca tcgatttaaa gatttggg 58

<210> 37
<211> 59
<212> DNA
<213> Artificial Sequence

<220>
<223> primer used in generation XhoI and ClaI
site in pPPC0006

<400> 37
aatcgatgag caacctcact cttgtgtgca tctcttttct cgaggctcct ggaataagc 59

<210> 38
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> primer used in generation XhoI and ClaI
site in pPPC0006
<400> 38
tacaaactta agagtccaat tagc 24

<210> 39
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> primer used in generation XhoI and ClaI
site in pPPC0006

<400> 39
cacttctcta gagtggtttc atatgtctt 29

<210> 40
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<221> Misc_Structure
<223> Synthetic oligonucleotide used to alter restriction
sites in pPPC0007

<400> 40
aagctgcctt aggcttataa taaggcgcgc cggccggccg tttaaactaa gcttaattct 60

<210> 41
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<221> Misc_Structure
<223> Synthetic oligonucleotide used to alter restriction
sites in pPPC0007

<400> 41
agaattaagc ttagtttaaa cggccggccg gcgcgcctta ttataagcct aaggcagctt 60

<210> 42
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> forward primer useful for generation of albumin fusion protein in which the albumin moiety is N-terminal of the Therapeutic Protein

<220>
<221> misc_feature
<222> (18)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (20)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (21)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (22)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (23)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (24)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (25)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (26)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (27)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (28)
<223> n equals a,t,g, or c

<220>

<221> misc_feature
<222> (29)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (30)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (31)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (32)
<223> n equals a,t,g, or c

<400> 42
aagctgcctt aggcttannn nnnnnnnnnn nn 32

<210> 43
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> reverse primer useful for generation of albumin fusion protein in which the albumin moiety is N-terminal of the Therapeutic Protein

<220>
<221> misc_feature
<222> (37)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (38)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (39)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (40)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (41)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (42)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (43)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (44)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (45)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (46)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (47)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (48)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (49)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (50)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (51)
<223> n equals a,t,g, or c

<400> 43
gcgcgcgttt aaacggccgg ccggcgcgcc ttattannnn nnnnnnnnnn n 51

<210> 44
<211> 4
<212> PRT
<213> Homo sapiens

<400> 44
Leu Asp Lys Arg
1

<210> 45
<211> 4

<212> PRT
<213> Homo sapiens

<400> 45
Leu Glu Lys Arg
  1

<210> 46
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> forward primer useful for generation of albumin fusion protein in which the albumin moiety is c-terminal of the Therapeutic Protein

<220>
<221> misc_feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (20)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (21)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (22)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (23)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (24)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (25)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (26)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (27)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (28)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (29)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (30)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (31)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (32)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (33)
<223> n equals a,t,g, or c

<400> 46
aggagcgtcg acaaaagann nnnnnnnnnn nnn 33

<210> 47
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<223> reverse primer useful for generation of albumin
fusion protein in which the albumin moiety is c-terminal of
the Therapeutic Protein

<220>
<221> misc_feature
<222> (38)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (39)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (40)
<223> n equals a,t,g, or c

<220>

<221> misc_feature
<222> (41)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (42)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (43)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (44)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (45)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (46)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (47)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (48)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (49)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (50)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (51)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (52)
<223> n equals a,t,g, or c

<400> 47
ctttaaatcg atgagcaacc tcactcttgt gtgcatcnnn nnnnnnnnnn nn 52

<210> 48
<211> 9
<212> PRT
<213> Homo sapiens

<400> 48
Asp Ala His Lys Ser Glu Val Ala His
1 5

<210> 49
<211> 11
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<222> (1) to (11)
<223> Kozak sequence

<400> 49
ccgccaccat g 11

<210> 50
<211> 46
<212> DNA
<213> Artificial Sequence

<220>
<223> forward primer useful for inserting Therapeutic protein into pC4:HSA vector

<220>
<221> misc_feature
<222> (29)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (30)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (31)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (32)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (33)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (34)

<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (35)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (36)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (37)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (38)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (39)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (40)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (41)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (42)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (43)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (44)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (45)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (46)
<223> n equals a,t,g, or c

<400> 50
ccgccgctcg aggggtgtgt ttcgtcgann nnnnnnnnnn nnnnnn 46

<210> 51
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
<223> reverse primer useful for inserting Therapeutic protein into pC4:HSA vector

<220>
<221> misc_feature
<222> (38)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (39)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (40)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (41)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (42)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (43)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (44)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (45)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (46)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (47)

<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (48)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (49)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (50)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (51)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (52)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (53)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (54)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (55)
<223> n equals a,t,g, or c

<400> 51
agtcccatcg atgagcaacc tcactcttgt gtgcatcnnn nnnnnnnnnn nnnnn 55

<210> 52
<211> 733
<212> DNA
<213> Homo sapiens

<400> 52
gggatccgga gcccaaatct tctgacaaaa ctcacacatg cccaccgtgc ccagcacctg 60
aattcgaggg tgcaccgtca gtcttcctct tcccccccaaa acccaaggac accctcatga 120
tctcccggac tcctgaggtc acatgcgtgg tggtggacgt aagccacgaa gaccctgagg 180
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 240
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 300
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca acccccatcg 360
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 420
catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 480
atccaagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 540

ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag ctcaccgtgg 600
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 660
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgagtg cgacggccgc 720
gactctagag gat 733

<210> 53
<211> 5
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (3)
<223> Xaa equals any of the twenty naturally ocurring L-amino acids

<400> 53
Trp Ser Xaa Trp Ser
1 5

<210> 54
<211> 86
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic sequence with 4 tandem copies of the GAS binding site found in the IRF1 promoter (Rothman et al., Immunity 1:457-468 (1994)), 18 nucleotides complementary to the SV40 early promoter, and a Xho I restriction site.

<400> 54
gcgcctcgag atttccccga aatctagatt tccccgaaat gatttccccg aaatgatttc 60
cccgaaatat ctgccatctc aattag 86

<210> 55
<211> 27
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic sequence complementary to the SV40 promter; includes a Hind III restriction site.

<400> 55
gcggcaagct ttttgcaaag cctaggc 27

<210> 56
<211> 271
<212> DNA
<213> Artificial Sequence

<220>
<221> Protein_Bind
<223> Synthetic promoter for use in biological assays; includes GAS binding sites found in the IRF1 promoter

<400> 56
ctcgagattt ccccgaaatc tagatttccc cgaaatgatt tccccgaaat gatttccccg 60
aaatatctgc catctcaatt agtcagcaac catagtcccg cccctaactc cgcccatccc 120

gcccctaact ccgcccagtt ccgcccattc tccgccccat ggctgactaa ttttttttat 180
ttatgcagag gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggctt 240
ttttggaggc ctaggctttt gcaaaaagct t 271

<210> 57
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer complementary to human genomic EGR-1 promoter sequence; includes a Xho I restriction site.

<400> 57
gcgctcgagg gatgacagcg atagaacccc gg 32

<210> 58
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer complementary to human genomic EGR-1 promoter sequence; includes a Hind III restriction site.

<400> 58
gcgaagcttc gcgactcccc ggatccgcct c 31

<210> 59
<211> 12
<212> DNA
<213> Homo sapiens

<400> 59
ggggactttc cc 12

<210> 60
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer with 4 tandem copies of the NF-KB binding site (GGGGACTTTCCC), 18 nucleotides complementary to the 5' end of the SV40 early promoter sequence, and a XhoI restriction site.

<400> 60
gcggcctcga ggggactttc ccggggactt tccggggact ttccgggact ttccatcctg 60
ccatctcaat tag 73

<210> 61
<211> 256
<212> DNA
<213> Artificial Sequence

<220>
<221> Protein_Bind
<223> Synthetic promoter for use in biological assays; includes NF-KB binding sites.

<400> 61

```
ctcgagggga ctttcccggg gactttccgg ggactttccg ggactttcca tctgccatct     60
caattagtca gcaaccatag tcccgcccct aactccgccc atcccgcccc taactccgcc    120
cagttccgcc cattctccgc cccatggctg actaattttt tttatttatg cagaggccga    180
ggccgcctcg gcctctgagc tattccagaa gtagtgagga ggcttttttg gaggcctagg    240
cttttgcaaa aagctt                                                    256
```

<210> 62
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 62
caggtgcagc tggtgcagtc tgg 23

<210> 63
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 63
caggtcaact taagggagtc tgg 23

<210> 64
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 64
gaggtgcagc tggtggagtc tgg 23

<210> 65
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 65
caggtgcagc tgcaggagtc ggg 23

<210> 66
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 66
gaggtgcagc tgttgcagtc tgc 23

<210> 67
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 67
caggtacagc tgcagcagtc agg 23

<210> 68
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 68
tgaggagacg gtgaccaggg tgcc 24

<210> 69
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 69
tgaagagacg gtgaccattg tccc 24

<210> 70
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 70
tgaggagacg gtgaccaggg ttcc 24

<210> 71
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 71
tgaggagacg gtgaccgtgg tccc 24

<210> 72
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 72
gacatccaga tgacccagtc tcc 23

<210> 73
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 73
gatgttgtga tgactcagtc tcc 23

<210> 74
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 74
gatattgtga tgactcagtc tcc 23

<210> 75
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 75
gaaattgtgt tgacgcagtc tcc 23

<210> 76
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 76
gacatcgtga tgacccagtc tcc 23

<210> 77
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 77
gaaacgacac tcacgcagtc tcc 23

<210> 78
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 78
gaaattgtgc tgactcagtc tcc 23

<210> 79
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 79
cagtctgtgt tgacgcagcc gcc 23

<210> 80
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 80
cagtctgccc tgactcagcc tgc 23

<210> 81
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 81
tcctatgtgc tgactcagcc acc 23

<210> 82
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 82
tcttctgagc tgactcagga ccc 23

<210> 83
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 83
cacgttatac tgactcaacc gcc 23

<210> 84
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 84
caggctgtgc tcactcagcc gtc 23

<210> 85
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 85
aattttatgc tgactcagcc cca 23

<210> 86
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jkappa reverse primer useful for

amplifying human VL domains

<400> 86
acgtttgatt tccaccttgg tccc 24

<210> 87
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 87
acgtttgatc tccagcttgg tccc 24

<210> 88
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 88
acgtttgata tccactttgg tccc 24

<210> 89
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 89
acgtttgatc tccaccttgg tccc 24

<210> 90
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 90
acgtttaatc tccagtcgtg tccc 24

<210> 91
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 91
cagtctgtgt tgacgcagcc gcc 23

<210> 92
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 92
cagtctgccc tgactcagcc tgc 23

<210> 93
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 93
tcctatgtgc tgactcagcc acc 23

<210> 94
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 94
tcttctgagc tgactcagga ccc 23

<210> 95
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 95
cacgttatac tgactcaacc gcc 23

<210> 96
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 96
caggctgtgc tcactcagcc gtc 23

<210> 97
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 97
aattttatgc tgactcagcc cca 23

<210> 98
<211> 5
<212> PRT
<213> Homo sapiens

<400> 98
Cys Asp Leu Pro Gln
1 5

<210> 99
<211> 165
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (23)
<223> Xaa equals Arg or Lys

<220>
<221> MISC_FEATURE
<222> (113)
<223> Xaa equals Ala or Val

<400> 99
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Xaa Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp Leu
65 70 75 80

Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
100 105 110

Xaa Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 100
<211> 165
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (23)
<223> Xaa equals Arg or Lys

<220>
<221> MISC_FEATURE
<222> (113)
<223> Xaa equals Ala or Val

<400> 100
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Xaa Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
100 105 110

Xaa Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 101
<211> 165
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (23)
<223> Xaa equals Arg or Lys

<400> 101
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Xaa Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Met Glu
85 90 95

Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met Asn
100 105 110

Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Lys Ile Phe Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 102
<211> 165
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (23)
<223> Xaa equals Arg or Lys

<220>
<221> MISC_FEATURE
<222> (97)
<223> Xaa equals Ser or Val

<220>

<221> MISC_FEATURE
<222> (98)
<223> Xaa equals Cys or Leu

<220>
<221> MISC_FEATURE
<222> (99)
<223> Xaa equals Val or Cys

<220>
<221> MISC_FEATURE
<222> (100)
<223> Xaa equals Met or Asp

<400> 102
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1   5   10   15

Leu Leu Ala Gln Met Arg Xaa Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95

Xaa Xaa Xaa Xaa Gln Glu Val Gly Val Ile Glu Ser Pro Leu Met Tyr
            100   105   110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125

Tyr Leu Thr Glu Lys Lys Tyr Ser Ser Cys Ala Trp Glu Val Val Arg
    130   135   140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Ile Asn Leu Gln Lys Arg
145   150   155   160

Leu Lys Ser Lys Glu
                165

<210> 103
<211> 167
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (115)
<223> Xaa equals Ala or Val

<400> 103
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1   5   10   15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ala Ala Trp Asp Glu
65 70 75 80

Asp Leu Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp
85 90 95

Leu Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu
100 105 110

Met Asn Xaa Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile
115 120 125

Thr Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
130 135 140

Val Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln
145 150 155 160

Glu Arg Leu Arg Arg Lys Glu
165

<210> 104
<211> 166
<212> PRT
<213> Homo sapiens

<400> 104
Met Cys Asp Leu Pro Glu Thr His Ser Leu Asp Asn Arg Arg Thr Leu
1 5 10 15

Met Leu Leu Ala Gln Met Ser Arg Ile Ser Pro Ser Ser Cys Leu Met
20 25 30

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln
35 40 45

Phe Gln Lys Ala Pro Ala Ile Ser Val Leu His Glu Leu Ile Gln Gln
50 55 60

Ile Phe Asn Leu Phe Thr Thr Lys Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

```
Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
    130                 135                 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160

Thr Gly Tyr Leu Arg Asn
                165
```

<210> 105
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic signal peptide

<400> 105

```
Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala Leu
  1               5                  10                  15

Trp Ala Pro Ala Arg Gly
         20
```

<210> 106
<211> 0
<212> DNA
<213> Artificial sequence

<220>
<223> primer (deleted)

<400> 106
000

<210> 107
<211> 106
<212> DNA
<213> Artificial sequence

<220>
<223> primer for full-length IFNb amplification, has BamHI cloning site

<400> 107

```
gcgcggatcc gaattccgcc gccatgacca acaagtgtct cctccaaatt gctctcctgt 60
tgtgcttctc cactacagct ctttccatga gctacaactt gcttgg                106
```

<210> 108
<211> 55
<212> DNA
<213> Artificial sequence

<220>
<223> primer for full-length IFNb amplification, has ClaI cloning site

<400> 108

```
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcgtt tcggaggtaa cctgt      55
```

<210> 109

<211> 41
<212> DNA
<213> Homo sapiens

<400> 109
cgcgcgcgtc gacaaaagat gtgatctgcc tcaaacccac a 41

<210> 110
<211> 59
<212> DNA
<213> Homo sapiens

<400> 110
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 111
<211> 21
<212> PRT
<213> Homo sapiens

<400> 111
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala
20

<210> 112
<211> 24
<212> PRT
<213> Homo sapiens

<400> 112
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Gly Ser Leu Asp Lys Arg
20

<210> 113
<211> 1497
<212> DNA
<213> Hypocrea jecorina

<400> 113
tctagagttg tgaagtcggt aatcccgctg tatagtaata cgagtcgcat ctaaatactc 60
cgaagctgct gcgaacccgg agaatcgaga tgtgctggaa agcttctagc gagcggctaa 120
attagcatga aaggctatga gaaattctgg agacggcttg ttgaatcatg gcgttccatt 180
cttcgacaag caaagcgttc cgtcgcagta gcaggcactc attcccgaaa aaactcggag 240
attcctaagt agcgatggaa ccggaataat ataataggca atacattgag ttgcctcgac 300
ggttgcaatg caggggtact gagcttggac ataactgttc cgtaccccac ctcttctcaa 360
cctttggcgt ttccctgatt cagcgtaccc gtacaagtcg taatcactat taacccagac 420
tgaccggacg tgttttgccc ttcatttgga gaaataatgt cattgcgatg tgtaatttgc 480
ctgcttgacc gactggggct gttcgaagcc cgaatgtagg attgttatcc gaactctgct 540
cgtagaggca tgttgtgaat ctgtgtcggg caggacacgc ctcgaaggtt cacggcaagg 600
gaaaccaccg atagcagtgt ctagtagcaa cctgtaaagc cgcaatgcag catcactgga 660
aaatacaaac caatggctaa aagtacataa gttaatgcct aaagaagtca tataccagcg 720
gctaataatt gtacaatcaa gtggctaaac gtaccgtaat ttgccaacgg cttgtggggt 780
tgcagaagca acggcaaagc cccacttccc cacgtttgtt tcttcactca gtccaatctc 840

agctggtgat cccccaattg ggtcgcttgt ttgttccggt gaagtgaaag aagacagagg 900
taagaatgtc tgactcggag cgttttgcat acaaccaagg gcagtgatgg aagacagtga 960
aatgttgaca ttcaaggagt atttagccag ggatgcttga gtgtatcgtg taaggaggtt 1020
tgtctgccga tacgacgaat actgtatagt cacttctggt gaagtggtcc atattgaaat 1080
gtaagtcggc actgaacagg caaaagattg agttgaaact gcctaagatc tcgggccctc 1140
gggccttcgg cctttgggtg tacatgtttg tgctccgggc aaatgcaaag tgtggtagga 1200
tcgaacacac tgctgccttt accaagcagc tgagggtatg tgataggcaa atgttcaggg 1260
gccactgcat ggtttcgaat agaaagagaa gcttagccaa gaacaatagc cgataaagat 1320
agcctcatta aacggaatga gctagtaggc aaagtcagcg aatgtgtata tataaaggtt 1380
cgaggtccgt gcctccctca tgctctcccc atctactcat caactcagat cctccaggag 1440
acttgtacac catcttttga ggcacagaaa cccaatagtc aaccgcggac tggcatc 1497

<210> 114
<211> 366
<212> DNA
<213> Aspergillus nidulans

<400> 114
agatctggtt cctgagtaca tctaccgatg cgcctcgatc cccctcttag ccgcatgaga 60
ttcctaccat ttatgtccta tcgttcaggg tcctatttgg accgctagaa atagactctg 120
ctcgatttgt ttccattatt cacgcaatta cgatagtatt tggctctttt cgtttggccc 180
aggtcaattc gggtaagacg cgatcacgcc attgtggccg ccggcgttgt gctgctgcta 240
ttccccgcat ataaacaacc cctccaccag ttcgttgggc tttgcgaatg ctgtactcta 300
tttcaagttg tcaaaagaga ggattcaaaa aattataccc cagatatcaa agatatcaaa 360
gccatc 366

<210> 115
<211> 1646
<212> DNA
<213> Hypocrea jecorina

<400> 115
tctagagttg tgaagtcggt aatcccgctg tatagtaata cgagtcgcat ctaaatactc 60
cgaagctgct gcgaacccgg agaatcgaga tgtgctggaa agcttctagc gagcggctaa 120
attagcatga aaggctatga gaaattctgg agacggcttg ttgaatcatg gcgttccatt 180
cttcgacaag caaagcgttc cgtcgcagta gcaggcactc attcccgaaa aaactcggag 240
attcctaagt agcgatggaa ccggaataat ataataggca atacattgag ttgcctcgac 300
ggttgcaatg caggggtact gagcttggac ataactgttc cgtaccccac ctcttctcaa 360
cctttggcgt ttccctgatt cagcgtaccc gtacaagtcg taatcactat taacccagac 420
tgaccggacg tgttttgccc ttcatttgga gaaataatgt cattgcgatg tgtaatttgc 480
ctgcttgacc gactggggct gttcgaagcc cgaatgtagg attgttatcc gaactctgct 540
cgtagaggca tgttgtgaat ctgtgtcggg caggacacgc ctcgaaggtt cacggcaagg 600
gaaaccaccg atagcagtgt ctagtagcaa cctgtaaagc cgcaatgcag catcactgga 660
aaatacaaac caatggctaa aagtacataa gttaatgcct aaagaagtca tataccagcg 720
gctaataatt gtacaatcaa gtggctaaac gtaccgtaat ttgccaacgg cttgtggggt 780
tgcagaagca acggcaaagc cccacttccc cacgtttgtt tcttcactca gtccaatctc 840
agctggtgat cccccaattg ggtcgcttgt ttgttccggt gaagtgaaag aagacagagg 900
taagaatgtc tgactcggag cgttttgcat acaaccaagg gcagtgatgg aagacagtga 960
aatgttgaca ttcaaggagt atttagccag ggatgcttga gtgtatcgtg taaggaggtt 1020
tgtctgccga tacgacgaat actgtatagt cacttctggt gaagtggtcc atattgaaat 1080
gtaagtcggc actgaacagg caaaagattg agttgaaact gcctaagatc tcgggccctc 1140
gggccttcgg cctttgggtg tacatgtttg tgctccgggc aaatgcaaag tgtggtagga 1200
tcgaacacac tgctgccttt accaagcagc tgagggtatg tgataggcaa atgttcaggg 1260
gccactgcat ggtttcgaat agaaagagaa gcttagcctg cagcctctta tcgagaaaga 1320
aattaccgtc gctcgtgatt tgtttgcaaa aagaacaaaa ctgaaaaaac ccagacacgc 1380
tcgacttcct gtcttcctat tgattgcagc ttccaatttc gtcacacaac aaggtcctag 1440
cttagccaag aacaatagcc gataaagata gcctcattaa acggaatgag ctagtaggca 1500
aagtcagcga atgtgtatat ataaaggttc gaggtccgtg cctccctcat gctctcccca 1560
tctactcatc aactcagatc ctccaggaga cttgtacacc atcttttgag gcacagaaac 1620

ccaatagtca accgcggact ggcatc 1646

<210> 116
<211> 516
<212> DNA
<213> Aspergillus nidulans

<400> 116
agatctggtt cctgagtaca tctaccgatg cgcctcgatc cccctcttag ccgcatgaga 60
ttcctaccat ttatgtccta tcgttcaggg tcctatttgg accgctagaa atagactctg 120
ctcgatttgt ttccattatt cacgcaatta cgatagtatt tggctctttt cgtttggccc 180
aggtcaattc gggtaagacg cgatcacgcc attgtggccg ccggcgctgc agcctcttat 240
cgagaaagaa attaccgtcg ctcgtgattt gtttgcaaaa agaacaaaac tgaaaaaacc 300
cagacacgct cgacttcctg tcttcctatt gattgcagct tccaatttcg tcacacaaca 360
aggtcctacg ccggcgttgt gctgctgcta ttccccgcat ataaacaacc cctccaccag 420
ttcgttgggc tttgcgaatg ctgtactcta tttcaagttg tcaaaagaga ggattcaaaa 480
aattataccc cagatatcaa agatatcaaa gccatc 516

<210> 117
<211> 495
<212> DNA
<213> Homo sapiens

<400> 117
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct tttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 118
<211> 495
<212> DNA
<213> Homo sapiens

<400> 118
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct tttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 119
<211> 495
<212> DNA
<213> Homo sapiens

<400> 119
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 120
<211> 498
<212> DNA
<213> Homo sapiens

<400> 120
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaataa 498

<210> 121
<211> 495
<212> DNA
<213> Homo sapiens

<400> 121
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 122
<211> 495
<212> DNA
<213> Homo sapiens

<400> 122
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 123
<211> 495

<212> DNA
<213> Homo sapiens

<400> 123
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct tttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 124
<211> 495
<212> DNA
<213> Homo sapiens

<400> 124
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct tttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 125
<211> 495
<212> DNA
<213> Homo sapiens

<400> 125
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct tttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 126
<211> 495
<212> DNA
<213> Homo sapiens

<400> 126
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 127
<211> 501
<212> DNA
<213> Homo sapiens

<400> 127
atgagctaca acttgcttgg attcctacaa agaagcagca attttcagtg tcagaagctc 60
ctgtggcaat tgaatgggag gcttgaatat tgcctcaagg acaggatgaa ctttgacatc 120
cctgaggaga ttaagcagct gcagcagttc cagaaggagg acgccgcatt gaccatctat 180
gagatgctcc agaacatctt tgctattttc agacaagatt catctagcac tggctggaat 240
gagactattg ttgagaacct cctggctaat gtctatcatc agataaacca tctgaagaca 300
gtcctggaag aaaaactgga gaaagaagat ttcaccaggg gaaaactcat gagcagtctg 360
cacctgaaaa gatattatgg gaggattctg cattacctga aggccaagga gtacagtcac 420
tgtgcctgga ccatagtcag agtggaaatc ctaaggaact tttacttcat taacagactt 480
acaggttacc tccgaaacta a 501

<210> 128
<211> 501
<212> DNA
<213> Homo sapiens

<400> 128
atgagctaca acttgcttgg attcctacaa agaagcagca attttcagtg tcagaagctc 60
ctgtggcaat tgaatgggag gcttgaatat tgcctcaagg acaggatgaa ctttgacatc 120
cctgaggaga ttaagcagct gcagcagttc cagaaggagg acgccgcatt gaccatctat 180
gagatgctcc agaacatctt tgctattttc agacaagatt catctagcac tggctggaat 240
gagactattg ttgagaacct cctggctaat gtctatcatc agataaacca tctgaagaca 300
gtcctggaag aaaaactgga gaaagaagat ttcaccaggg gaaaactcat gagcagtctg 360
cacctgaaaa gatattatgg gaggattctg cattacctga aggccaagga gtacagtcac 420
tgtgcctgga ccatagtcag agtggaaatc ctaaggaact tttacttcat taacagactt 480
acaggttacc tccgaaacta a 501

<210> 129
<211> 561
<212> DNA
<213> Homo sapiens

<400> 129
atgaccaaca agtgtctcct ccaaattgct ctcctgttgt gcttctccac tacagctctt 60
tccatgagct acaacttgct tggattccta caaagaagca gcaattttca gtgtcagaag 120
ctcctgtggc aattgaatgg gaggcttgaa tattgcctca aggacaggat gaactttgac 180
atccctgagg agattaagca gctgcagcag ttccagaagg aggacgccgc attgaccatc 240
tatgagatgc tccagaacat ctttgctatt ttcagacaag attcatctag cactggctgg 300
aatgagacta ttgttgagaa cctcctggct aatgtctatc atcagataaa ccatctgaag 360
acagtcctgg aagaaaaact ggagaaagaa gatttcacca ggggaaaact catgagcagt 420
ctgcacctga aaagatatta tgggaggatt ctgcattacc tgaaggccaa ggagtacagt 480
cactgtgcct ggaccatagt cagagtggaa atcctaagga acttttactt cattaacaga 540
cttacaggtt acctccgaaa c 561

<210> 130
<211> 498
<212> DNA
<213> Homo sapiens

<400> 130
atgagctaca acttgcttgg attcctacaa agaagcagca attttcagtg tcagaagctc 60
ctgtggcaat tgaatgggag gcttgaatat tgcctcaagg acaggatgaa ctttgacatc 120
cctgaggaga ttaagcagct gcagcagttc cagaaggagg acgccgcatt gaccatctat 180
gagatgctcc agaacatctt tgctattttc agacaagatt catctagcac tggctggaat 240
gagactattg ttgagaacct cctggctaat gtctatcatc agataaacca tctgaagaca 300
gtcctggaag aaaaactgga gaaagaagat ttcaccaggg gaaaactcat gagcagtctg 360
cacctgaaaa gatattatgg gaggattctg cattacctga aggccaagga gtacagtcac 420
tgtgcctgga ccatagtcag agtggaaatc ctaaggaact tttacttcat taacagactt 480
acaggttacc tccgaaac 498

<210> 131
<211> 561
<212> DNA
<213> Homo sapiens

<400> 131
atgaccaaca agtgtctcct ccaaattgct ctcctgttgt gcttctccac tacagctctt 60
tccatgagct acaacttgct tggattccta caaagaagca gcaattttca gtgtcagaag 120
ctcctgtggc aattgaatgg gaggcttgaa tattgcctca aggacaggat gaactttgac 180
atccctgagg agattaagca gctgcagcag ttccagaagg aggacgccgc attgaccatc 240
tatgagatgc tccagaacat ctttgctatt ttcagacaag attcatctag cactggctgg 300
aatgagacta ttgttgagaa cctcctggct aatgtctatc atcagataaa ccatctgaag 360
acagtcctgg aagaaaaact ggagaaagaa gatttcacca ggggaaaact catgagcagt 420
ctgcacctga aaagatatta tgggaggatt ctgcattacc tgaaggccaa ggagtacagt 480
cactgtgcct ggaccatagt cagagtggaa atcctaagga acttttactt cattaacaga 540
cttacaggtt acctccgaaa c 561

<210> 132
<211> 501
<212> DNA
<213> Homo sapiens

<400> 132
atgagctaca acttgcttgg attcctacaa agaagcagca attttcagtg tcagaagctc 60
ctgtggcaat tgaatgggag gcttgaatat tgcctcaagg acaggatgaa ctttgacatc 120
cctgaggaga ttaagcagct gcagcagttc cagaaggagg acgccgcatt gaccatctat 180
gagatgctcc agaacatctt tgctattttc agacaagatt catctagcac tggctggaat 240
gagactattg ttgagaacct cctggctaat gtctatcatc agataaacca tctgaagaca 300
gtcctggaag aaaaactgga gaaagaagat ttcaccaggg gaaaactcat gagcagtctg 360
cacctgaaaa gatattatgg gaggattctg cattacctga aggccaagga gtacagtcac 420
tgtgcctgga ccatagtcag agtggaaatc ctaaggaact tttacttcat taacagactt 480
acaggttacc tccgaaacta a 501

<210> 133
<211> 561
<212> DNA
<213> Homo sapiens

<400> 133
atgaccaaca agtgtctcct ccaaattgct ctcctgttgt gcttctccac tacagctctt 60
tccatgagct acaacttgct tggattccta caaagaagca gcaattttca gtgtcagaag 120
ctcctgtggc aattgaatgg gaggcttgaa tattgcctca aggacaggat gaactttgac 180
atccctgagg agattaagca gctgcagcag ttccagaagg aggacgccgc attgaccatc 240
tatgagatgc tccagaacat ctttgctatt ttcagacaag attcatctag cactggctgg 300
aatgagacta ttgttgagaa cctcctggct aatgtctatc atcagataaa ccatctgaag 360
acagtcctgg aagaaaaact ggagaaagaa gatttcacca ggggaaaact catgagcagt 420
ctgcacctga aaagatatta tgggaggatt ctgcattacc tgaaggccaa ggagtacagt 480

cactgtgcct ggaccatagt cagagtggaa atcctaagga acttttactt cattaacaga 540
cttacaggtt acctccgaaa c 561

<210> 134
<211> 561
<212> DNA
<213> Homo sapiens

<400> 134
atgaccaaca agtgtctcct ccaaattgct ctcctgttgt gcttctccac tacagctctt 60
tccatgagct acaacttgct tggattccta caaagaagca gcaattttca gtgtcagaag 120
ctcctgtggc aattgaatgg gaggcttgaa tattgcctca aggacaggat gaactttgac 180
atccctgagg agattaagca gctgcagcag ttccagaagg aggacgccgc attgaccatc 240
tatgagatgc tccagaacat ctttgctatt ttcagacaag attcatctag cactggctgg 300
aatgagacta ttgttgagaa cctcctggct aatgtctatc atcagataaa ccatctgaag 360
acagtcctgg aagaaaaact ggagaaagaa gatttcacca ggggaaaact catgagcagt 420
ctgcacctga aaagatatta tgggaggatt ctgcattacc tgaaggccaa ggagtacagt 480
cactgtgcct ggaccatagt cagagtggaa atcctaagga acttttactt cattaacaga 540
cttacaggtt acctccgaaa c 561

<210> 135
<211> 498
<212> DNA
<213> Homo sapiens

<400> 135
atgagctaca acttgcttgg attcctacaa agaagcagca attttcagtg tcagaagctc 60
ctgtggcaat tgaatgggag gcttgaatat tgcctcaagg acaggatgaa ctttgacatc 120
cctgaggaga ttaagcagct gcagcagttc cagaaggagg acgccgcatt gaccatctat 180
gagatgctcc agaacatctt tgctattttc agacaagatt catctagcac tggctggaat 240
gagactattg ttgagaacct cctggctaat gtctatcatc agataaacca tctgaagaca 300
gtcctggaag aaaaactgga gaaagaagat ttcaccaggg gaaaactcat gagcagtctg 360
cacctgaaaa gatattatgg gaggattctg cattacctga aggccaagga gtacagtcac 420
tgtgcctgga ccatagtcag agtggaaatc ctaaggaact tttacttcat taacagactt 480
acaggttacc tccgaaac 498

<210> 136
<211> 498
<212> DNA
<213> Homo sapiens

<400> 136
atgagctaca acttgcttgg attcctacaa agaagcagca attttcagtg tcagaagctc 60
ctgtggcaat tgaatgggag gcttgaatat tgcctcaagg acaggatgaa ctttgacatc 120
cctgaggaga ttaagcagct gcagcagttc cagaaggagg acgccgcatt gaccatctat 180
gagatgctcc agaacatctt tgctattttc agacaagatt catctagcac tggctggaat 240
gagactattg ttgagaacct cctggctaat gtctatcatc agataaacca tctgaagaca 300
gtcctggaag aaaaactgga gaaagaagat ttcaccaggg gaaaactcat gagcagtctg 360
cacctgaaaa gatattatgg gaggattctg cattacctga aggccaagga gtacagtcac 420
tgtgcctgga ccatagtcag agtggaaatc ctaaggaact tttacttcat taacagactt 480
acaggttacc tccgaaac 498

<210> 137
<211> 498
<212> DNA
<213> Homo sapiens

<400> 137
atgagctaca acttgcttgg attcctacaa agaagcagca attttcagtg tcagaagctc 60
ctgtggcaat tgaatgggag gcttgaatat tgcctcaagg acaggatgaa ctttgacatc 120
cctgaggaga ttaagcagct gcagcagttc cagaaggagg acgccgcatt gaccatctat 180
gagatgctcc agaacatctt tgctattttc agacaagatt catctagcac tggctggaat 240
gagactattg ttgagaacct cctggctaat gtctatcatc agataaacca tctgaagaca 300
gtcctggaag aaaaactgga gaaagaagat ttcaccaggg gaaaactcat gagcagtctg 360
cacctgaaaa gatattatgg gaggattctg cattacctga aggccaagga gtacagtcac 420
tgtgcctgga ccatagtcag agtggaaatc ctaaggaact tttacttcat taacagactt 480
acaggttacc tccgaaac 498

<210> 138
<211> 495
<212> DNA
<213> Homo sapiens

<400> 138
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acttggaagc ctgtgtgatg 300
caggaggaga gggtgggaga aactcccctg atgaatgcgg actccatctt ggctgtgaag 360
aaatacttcc gaagaatcac tctctatctg acagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatcc ctctctttat caacaaactt gcaagaaaga 480
ttaaggagga aggaa 495

<210> 139
<211> 495
<212> DNA
<213> Homo sapiens

<400> 139
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggagtc ctgtgtgatg 300
caggaagtgg gggtgataga gtctcccctg atgtacgagg actccatcct ggctgtgagg 360
aaatacttcc aaagaatcac tctatatctg acagagaaga aatacagctc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatcc ttctctttat caatcaactt gcaaaaaaga 480
ttgaagagta aggaa 495

<210> 140
<211> 495
<212> DNA
<213> Homo sapiens

<400> 140
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acatggaagc ctgcgtgata 300
caggaggttg gggtggaaga gactcccctg atgaatgtgg actccatctt ggctgtgaag 360
aaatacttcc aaagaatcac tctttatctg acagagaaga aatacagccc ttgtgcttgg 420
gaggttgtca gagcagaaat catgagatcc ttctctttat caaaaatttt tcaagaaaga 480
ttaaggagga aggaa 495

<210> 141
<211> 495
<212> DNA
<213> Homo sapiens

<400> 141
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaacctctt taccacaaaa gattcatctg ctgcttggga tgaggacctc 240
ctagacaaat tctgcaccga actctaccag cagctgaatg acttggaagc ctgtgtgatg 300
caggaggaga gggtgggaga aactcccctg atgaatgcgg actccatctt ggctgtgaag 360
aaatacttcc gaagaatcac tctctatctg acagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatcc ctctctttat caacaaactt gcaagaaaga 480
ttaaggagga aggaa 495

<210> 142
<211> 495
<212> DNA
<213> Homo sapiens

<400> 142
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acttggaagc ctgtgtgatg 300
caggaggaga gggtgggaga aactcccctg atgaatgcgg actccatctt ggctgtgaag 360
aaatacttcc gaagaatcac tctctatctg acagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatcc ctctctttat caacaaactt gcaagaaaga 480
ttaaggagga aggaa 495

<210> 143
<211> 462
<212> DNA
<213> Homo sapiens

<400> 143
atgtacagga tgcaactcct gtcttgcatt gcactaagtc ttgcacttgt cacaaacagt 60
gcacctactt caagttctac aaagaaaaca cagctacaac tggagcattt actgctggat 120
ttacagatga ttttgaatgg aattaataat tacaagaatc ccaaactcac caggatgctc 180
acatttaagt tttacatgcc caagaaggcc acagaactga aacatcttca gtgtctagaa 240
gaagaactca aacctctgga ggaagtgcta aatttagctc aaagcaaaaa ctttcactta 300
agacccaggg acttaatcag caatatcaac gtaatagttc tggaactaaa gggatctgaa 360
acaacattca tgtgtgaata tgctgatgag acagcaacca ttgtagaatt tctgaacaga 420
tggattacct tttgtcaaag catcatctca acactgactt ga 462

<210> 144
<211> 462
<212> DNA
<213> Homo sapiens

<400> 144
atgtacagga tgcaactcct gtcttgcatt gcactaagtc ttgcacttgt cacaaacagt 60
gcacctactt caagttctac aaagaaaaca cagctacaac tggagcattt actgctggat 120
ttacagatga ttttgaatgg aattaataat tacaagaatc ccaaactcac caggatgctc 180

acatttaagt tttacatgcc caagaaggcc acagaactga aacatcttca gtgtctagaa 240
gaagaactca aacctctgga ggaagtgcta aatttagctc aaagcaaaaa ctttcactta 300
agacccaggg acttaatcag caatatcaac gtaatagttc tggaactaaa gggatctgaa 360
acaacattca tgtgtgaata tgctgatgag acagcaacca ttgtagaatt tctgaacaga 420
tggattacct tttgtcaaag catcatctca acactgactt ga 462

<210> 145
<211> 462
<212> DNA
<213> Homo sapiens

<400> 145
atgtacagga tgcaactcct gtcttgcatt gcactaagtc ttgcacttgt cacaaacagt 60
gcacctactt caagttctac aaagaaaaca cagctacaac tggagcattt actgctggat 120
ttacagatga ttttgaatgg aattaataat tacaagaatc ccaaactcac caggatgctc 180
acatttaagt tttacatgcc caagaaggcc acagaactga aacatcttca gtgtctagaa 240
gaagaactca aacctctgga ggaagtgcta aatttagctc aaagcaaaaa ctttcactta 300
agacccaggg acttaatcag caatatcaac gtaatagttc tggaactaaa gggatctgaa 360
acaacattca tgtgtgaata tgctgatgag acagcaacca ttgtagaatt tctgaacaga 420
tggattacct tttgtcaaag catcatctca acactgactt ga 462

<210> 146
<211> 462
<212> DNA
<213> Homo sapiens

<400> 146
atgtacagga tgcaactcct gtcttgcatt gcactaagtc ttgcacttgt cacaaacagt 60
gcacctactt caagttctac aaagaaaaca cagctacaac tggagcattt actgctggat 120
ttacagatga ttttgaatgg aattaataat tacaagaatc ccaaactcac caggatgctc 180
acatttaagt tttacatgcc caagaaggcc acagaactga aacatcttca gtgtctagaa 240
gaagaactca aacctctgga ggaagtgcta aatttagctc aaagcaaaaa ctttcactta 300
agacccaggg acttaatcag caatatcaac gtaatagttc tggaactaaa gggatctgaa 360
acaacattca tgtgtgaata tgctgatgag acagcaacca ttgtagaatt tctgaacaga 420
tggattacct tttgtcaaag catcatctca acactgactt ga 462

<210> 147
<211> 453
<212> DNA
<213> Homo sapiens

<400> 147
atgcaactcc tgtcttgcat tgcactaagt cttgcacttg tcacaaacag tgcacctact 60
tcaagttcta caaagaaaac acagctacaa ctggagcatt tactgctgga tttacagatg 120
attttgaatg gaattaataa ttacaagaat cccaaactca ccaggatgct cacatttaag 180
ttttacatgc ccaagaaggc cacagaactg aaacatcttc agtgtctaga agaagaactc 240
aaacctctgg aggaagtgct aaatttagct caaagcaaaa actttcactt aagacccagg 300
gacttaatca gcaatatcaa cgtaatagtt ctggaactaa agggatctga aacaacattc 360
atgtgtgaat atgctgatga gacagcaacc attgtagaat ttctgaacag atggattacc 420
ttttctcaga gcatcatctc aacactgact tga 453

<210> 148
<211> 453
<212> DNA
<213> Homo sapiens

<400> 148

```
atgcaactcc tgtcttgcat tgcactaagt cttgcacttg tcacaaacag tgcacctact      60
tcaagttcta caaagaaaac acagctacaa ctggagcatt tactgctgga tttacagatg     120
attttgaatg gaattaataa ttacaagaat cccaaactca ccaggatgct cacatttaag     180
ttttacatgc ccaagaaggc cacagaactg aaacatcttc agtgtctaga agaagaactc     240
aaacctctgg aggaagtgct aaatttagct caaagcaaaa actttcactt aagacccagg     300
gacttaatca gcaatatcaa cgtaatagtt ctggaactaa agggatctga aacaacattc     360
atgtgtgaat atgctgatga gacagcaacc attgtagaat ttctgaacag atggattacc     420
ttttctcaga gcatcatctc aacactgact tga                                  453
```

```
<210> 149
<211> 767
<212> PRT
<213> Homo sapiens

<400> 149
Met Phe Lys Ser Val Val Tyr Ser Ile Leu Ala Ala Ser Leu Ala Asn
1               5                   10                  15

Ala Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
            20                  25                  30

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
        35                  40                  45

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
    50                  55                  60

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
65                  70                  75                  80

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
                85                  90                  95

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
            100                 105                 110

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
        115                 120                 125

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
    130                 135                 140

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
145                 150                 155                 160

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
                165                 170                 175

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
            180                 185                 190

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
        195                 200                 205

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
    210                 215                 220

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
225                 230                 235                 240
```

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
245 250 255

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
260 265 270

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
275 280 285

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
290 295 300

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
305 310 315 320

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
325 330 335

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
340 345 350

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
355 360 365

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
370 375 380

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
385 390 395 400

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
405 410 415

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
420 425 430

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
435 440 445

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
450 455 460

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
465 470 475 480

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
485 490 495

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
500 505 510

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
515 520 525

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
530 535 540

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
545 550 555 560

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys

565 570 575

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
580 585 590

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Cys Asp Leu Pro Gln Thr
595 600 605

His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg
610 615 620

Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe
625 630 635 640

Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro
645 650 655

Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys
660 665 670

Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr
675 680 685

Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly
690 695 700

Val Gly Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala
705 710 715 720

Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys
725 730 735

Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser
740 745 750

Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu
755 760 765

<210> 150
<211> 769
<212> PRT
<213> Homo sapiens

<400> 150
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
20 25 30

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
35 40 45

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
50 55 60

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
65 70 75 80

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val

85 90 95

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
100 105 110

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
115 120 125

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
130 135 140

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
145 150 155 160

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
165 170 175

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
180 185 190

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
195 200 205

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
210 215 220

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
225 230 235 240

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
245 250 255

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
260 265 270

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
275 280 285

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
290 295 300

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
305 310 315 320

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
325 330 335

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
340 345 350

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
355 360 365

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
370 375 380

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
385 390 395 400

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
405 410 415

```
Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
        420                 425                 430

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
        435                 440                 445

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
    450                 455                 460

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
465                 470                 475                 480

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
                485                 490                 495

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
            500                 505                 510

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
        515                 520                 525

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
    530                 535                 540

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
545                 550                 555                 560

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
                565                 570                 575

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
            580                 585                 590

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Cys Asp Leu Pro
        595                 600                 605

Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln
    610                 615                 620

Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe
625                 630                 635                 640

Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr
                645                 650                 655

Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser
            660                 665                 670

Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe
        675                 680                 685

Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile
    690                 695                 700

Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile
705                 710                 715                 720

Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu
                725                 730                 735
```

Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met
740 745 750

Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys
755 760 765

Glu

<210> 151
<211> 779
<212> PRT
<213> Homo sapiens

<400> 151
Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1 5 10 15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg Asp Ala His
20 25 30

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
35 40 45

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
50 55 60

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
65 70 75 80

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
85 90 95

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
100 105 110

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
115 120 125

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
130 135 140

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
145 150 155 160

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
165 170 175

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
180 185 190

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
195 200 205

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
210 215 220

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
225 230 235 240

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
245 250 255

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
260 265 270

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
275 280 285

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
290 295 300

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
305 310 315 320

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
325 330 335

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
340 345 350

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
355 360 365

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
370 375 380

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
385 390 395 400

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
405 410 415

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
420 425 430

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
435 440 445

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
450 455 460

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
465 470 475 480

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
485 490 495

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
500 505 510

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
515 520 525

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
530 535 540

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
545 550 555 560

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val

565 570 575

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
580 585 590

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
595 600 605

Gln Ala Ala Leu Gly Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly
610 615 620

Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu
625 630 635 640

Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu
645 650 655

Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu
660 665 670

Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala
675 680 685

Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln
690 695 700

Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr
705 710 715 720

Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr
725 730 735

Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys
740 745 750

Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser
755 760 765

Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu
770 775

<210> 152
<211> 774
<212> PRT
<213> Homo sapiens

<400> 152
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Cys Asp Leu Pro Gln Thr His Ser
20 25 30

Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile
35 40 45

Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln
50 55 60

Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu

```
65                  70                  75                  80

His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser
                85                  90                  95

Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu
            100                 105                 110

Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly
        115                 120                 125

Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg
    130                 135                 140

Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser
145                 150                 155                 160

Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser
                165                 170                 175

Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His
            180                 185                 190

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
        195                 200                 205

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
    210                 215                 220

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
225                 230                 235                 240

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
                245                 250                 255

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
            260                 265                 270

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
        275                 280                 285

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
    290                 295                 300

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
305                 310                 315                 320

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
                325                 330                 335

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
            340                 345                 350

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
        355                 360                 365

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
    370                 375                 380

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
385                 390                 395                 400
```

```
Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
                405                 410                 415

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
            420                 425                 430

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
        435                 440                 445

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
    450                 455                 460

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
465                 470                 475                 480

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
                485                 490                 495

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
            500                 505                 510

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
        515                 520                 525

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
    530                 535                 540

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
545                 550                 555                 560

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
                565                 570                 575

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
            580                 585                 590

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
        595                 600                 605

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
    610                 615                 620

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
625                 630                 635                 640

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
                645                 650                 655

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
            660                 665                 670

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
        675                 680                 685

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
    690                 695                 700

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
705                 710                 715                 720
```

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
725 730 735

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
740 745 750

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
755 760 765

Gln Ala Ala Leu Gly Leu
770

<210> 153
<211> 769
<212> PRT
<213> Homo sapiens

<400> 153
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
20 25 30

Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys
35 40 45

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
50 55 60

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
65 70 75 80

Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
85 90 95

Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
100 105 110

Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro
115 120 125

Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
130 135 140

Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
145 150 155 160

Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu
165 170 175

Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys Ser Glu Val Ala
180 185 190

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
195 200 205

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
210 215 220

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
225 230 235 240

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
245 250 255

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
260 265 270

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
275 280 285

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
290 295 300

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
305 310 315 320

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
325 330 335

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
340 345 350

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
355 360 365

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
370 375 380

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
385 390 395 400

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
405 410 415

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
420 425 430

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
435 440 445

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
450 455 460

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
465 470 475 480

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
485 490 495

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
500 505 510

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
515 520 525

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
530 535 540

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu

545 550 555 560

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
565 570 575

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
580 585 590

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
595 600 605

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
610 615 620

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
625 630 635 640

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
645 650 655

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
660 665 670

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
675 680 685

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
690 695 700

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
705 710 715 720

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
725 730 735

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
740 745 750

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
755 760 765

Leu

<210> 154
<211> 835
<212> PRT
<213> Homo sapiens

<400> 154
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
1 5 10 15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
20 25 30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
35 40 45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
50 55 60

```
Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65                  70                  75                  80

Ser Leu Asp Lys Arg Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser
                85                  90                  95

Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe
            100                 105                 110

Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe
        115                 120                 125

Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met
    130                 135                 140

Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala
145                 150                 155                 160

Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln
                165                 170                 175

Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu
            180                 185                 190

Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe
        195                 200                 205

Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala
    210                 215                 220

Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr
225                 230                 235                 240

Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys Ser Glu
                245                 250                 255

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
            260                 265                 270

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
        275                 280                 285

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
    290                 295                 300

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
305                 310                 315                 320

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
                325                 330                 335

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
            340                 345                 350

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
        355                 360                 365

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
    370                 375                 380
```

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
385 390 395 400

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
405 410 415

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
420 425 430

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
435 440 445

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
450 455 460

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
465 470 475 480

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
485 490 495

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
500 505 510

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
515 520 525

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
530 535 540

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
545 550 555 560

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
565 570 575

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
580 585 590

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
595 600 605

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
610 615 620

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
625 630 635 640

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
645 650 655

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
660 665 670

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
675 680 685

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
690 695 700

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser

705 710 715 720

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
725 730 735

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
740 745 750

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
755 760 765

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
770 775 780

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
785 790 795 800

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
805 810 815

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
820 825 830

Leu Gly Leu
835

<210> 155
<211> 774
<212> PRT
<213> Homo sapiens

<400> 155
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys

```
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480
```

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705 710 715 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
725 730 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Ser Leu Arg Ser Lys Glu
770

<210> 156
<211> 773

<212> PRT
<213> Homo sapiens

<400> 156
Met Ala Leu Thr Phe Ala Leu Leu Val Ala Leu Leu Val Leu Ser Cys
1   5   10   15

Lys Ser Ser Cys Ser Val Gly Cys Asp Leu Pro Gln Thr His Ser Leu
            20   25   30

Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser
        35   40   45

Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu
    50   55   60

Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His
65   70   75   80

Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser
                85   90   95

Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr
            100   105   110

Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val
        115   120   125

Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys
    130   135   140

Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro
145   150   155   160

Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu
                165   170   175

Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys
            180   185   190

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
        195   200   205

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
    210   215   220

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
225   230   235   240

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
                245   250   255

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
            260   265   270

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
        275   280   285

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
    290   295   300

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
305 310 315 320

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
325 330 335

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
340 345 350

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
355 360 365

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
370 375 380

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
385 390 395 400

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
405 410 415

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
420 425 430

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
435 440 445

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
450 455 460

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
465 470 475 480

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
485 490 495

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
500 505 510

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
515 520 525

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
530 535 540

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
545 550 555 560

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
565 570 575

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
580 585 590

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
595 600 605

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
610 615 620

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr

625 630 635 640

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
645 650 655

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
660 665 670

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
675 680 685

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
690 695 700

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
705 710 715 720

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
725 730 735

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
740 745 750

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
755 760 765

Ala Ala Leu Gly Leu
770

<210> 157
<211> 769
<212> PRT
<213> Homo sapiens

<400> 157
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
20 25 30

Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys
35 40 45

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
50 55 60

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
65 70 75 80

Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
85 90 95

Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
100 105 110

Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro
115 120 125

Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg

130 135 140

Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
145 150 155 160

Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu
165 170 175

Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys Ser Glu Val Ala
180 185 190

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
195 200 205

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
210 215 220

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
225 230 235 240

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
245 250 255

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
260 265 270

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
275 280 285

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
290 295 300

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
305 310 315 320

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
325 330 335

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
340 345 350

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
355 360 365

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
370 375 380

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
385 390 395 400

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
405 410 415

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
420 425 430

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
435 440 445

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
450 455 460

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
465 470 475 480

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
485 490 495

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
500 505 510

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
515 520 525

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
530 535 540

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
545 550 555 560

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
565 570 575

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
580 585 590

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
595 600 605

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
610 615 620

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
625 630 635 640

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
645 650 655

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
660 665 670

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
675 680 685

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
690 695 700

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
705 710 715 720

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
725 730 735

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
740 745 750

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
755 760 765

Leu

<210> 158
<211> 774
<212> PRT
<213> Homo sapiens

<400> 158
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20   25   30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35   40   45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50   55   60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65   70   75   80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85   90   95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100   105   110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115   120   125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130   135   140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145   150   155   160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165   170   175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180   185   190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195   200   205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210   215   220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225   230   235   240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245   250   255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260   265   270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275   280   285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu

290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705 710 715 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
725 730 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Ser Leu Arg Ser Lys Glu
770

<210> 159
<211> 775
<212> PRT
<213> Homo sapiens

<400> 159
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Met Ser Tyr Asn Leu Leu Gly Phe
20 25 30

Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu
35 40 45

Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile
50 55 60

Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala
65 70 75 80

Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln
85 90 95

Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu
100 105 110

Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu
115 120 125

Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu
130 135 140

His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys
145 150 155 160

Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg
165 170 175

Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala
180 185 190

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
195 200 205

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
210 215 220

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
225 230 235 240

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
245 250 255

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
260 265 270

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
275 280 285

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
290 295 300

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
305 310 315 320

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
325 330 335

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
340 345 350

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
355 360 365

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
370 375 380

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
385 390 395 400

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
405 410 415

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
420 425 430

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
435 440 445

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
450 455 460

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
465 470 475 480

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
485 490 495

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
500 505 510

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
515 520 525

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
530 535 540

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
545 550 555 560

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
565 570 575

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
580 585 590

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
595 600 605

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
610 615 620

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
625 630 635 640

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
645 650 655

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
660 665 670

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
675 680 685

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
690 695 700

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
705 710 715 720

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
725 730 735

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
740 745 750

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
755 760 765

Ser Gln Ala Ala Leu Gly Leu

770 775

<210> 160
<211> 775
<212> PRT
<213> Homo sapiens

<400> 160
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile

275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe
610 615 620

Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys
625 630 635 640

Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu
645 650 655

Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu
660 665 670

Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp
675 680 685

Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile
690 695 700

Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe
705 710 715 720

Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly
725 730 735

Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp
740 745 750

Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg
755 760 765

Leu Thr Gly Tyr Leu Arg Asn
770 775

<210> 161
<211> 772
<212> PRT
<213> Homo sapiens

<400> 161
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
35 40 45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
50 55 60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65 70 75 80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
85 90 95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
100 105 110

```
Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
        115                 120                 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
    130                 135                 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145                 150                 155                 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
                165                 170                 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala His Lys Ser
            180                 185                 190

Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala
        195                 200                 205

Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu
    210                 215                 220

Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys
225                 230                 235                 240

Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu
                245                 250                 255

Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly
            260                 265                 270

Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys
        275                 280                 285

Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg
    290                 295                 300

Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr
305                 310                 315                 320

Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe
                325                 330                 335

Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe
            340                 345                 350

Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys
        355                 360                 365

Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg
    370                 375                 380

Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
385                 390                 395                 400

Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala
                405                 410                 415

Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys
            420                 425                 430
```

```
Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala
        435                 440                 445

Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu
    450                 455                 460

Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val
465                 470                 475                 480

Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe
                485                 490                 495

Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
            500                 505                 510

Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr
        515                 520                 525

Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu
    530                 535                 540

Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val
545                 550                 555                 560

Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys
                565                 570                 575

Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn
            580                 585                 590

Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro
        595                 600                 605

Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys
    610                 615                 620

Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu
625                 630                 635                 640

Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val
                645                 650                 655

Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg
            660                 665                 670

Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu
        675                 680                 685

Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser
    690                 695                 700

Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val
705                 710                 715                 720

Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp
                725                 730                 735

Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu
            740                 745                 750

Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala
```

755 760 765

Ala Leu Gly Leu
770

<210> 162
<211> 775
<212> PRT
<213> Homo sapiens

<400> 162
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly

260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe
610 615 620

Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys
625 630 635 640

Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu
645 650 655

Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu
660 665 670

Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp
675 680 685

Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile
690 695 700

Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe
705 710 715 720

Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly
725 730 735

Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp
740 745 750

Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg
755 760 765

Leu Thr Gly Tyr Leu Arg Asn
770 775

<210> 163
<211> 772
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (240)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> MISC_FEATURE
<222> (270)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 163
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg

```
        35                  40                  45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
    50                  55                  60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65                  70                  75                  80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
                85                  90                  95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
            100                 105                 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
        115                 120                 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
    130                 135                 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145                 150                 155                 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
                165                 170                 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala His Lys Ser
            180                 185                 190

Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala
        195                 200                 205

Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu
    210                 215                 220

Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Xaa
225                 230                 235                 240

Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu
                245                 250                 255

Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Xaa Tyr Gly
            260                 265                 270

Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys
        275                 280                 285

Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg
    290                 295                 300

Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr
305                 310                 315                 320

Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe
                325                 330                 335

Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe
            340                 345                 350

Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys
        355                 360                 365
```

Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg
370 375 380

Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
385 390 395 400

Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala
405 410 415

Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys
420 425 430

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala
435 440 445

Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu
450 455 460

Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val
465 470 475 480

Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe
485 490 495

Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
500 505 510

Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr
515 520 525

Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu
530 535 540

Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val
545 550 555 560

Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys
565 570 575

Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn
580 585 590

Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro
595 600 605

Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys
610 615 620

Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu
625 630 635 640

Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val
645 650 655

Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg
660 665 670

Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu
675 680 685

Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser
    690   695   700

Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val
705   710   715   720

Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp
                725   730   735

Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu
            740   745   750

Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala
        755   760   765

Ala Leu Gly Leu
    770

<210> 164
<211> 775
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (487)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 164
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20   25   30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35   40   45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50   55   60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65   70   75   80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85   90   95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100   105   110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115   120   125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130   135   140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145   150   155   160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro

165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Xaa His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe
610 615 620

Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys
625 630 635 640

Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu
645 650 655

Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu
660 665 670

Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp
675 680 685

Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile
690 695 700

Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe
705 710 715 720

Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly
725 730 735

Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp
740 745 750

Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg
755 760 765

Leu Thr Gly Tyr Leu Arg Asn
770 775

<210> 165
<211> 771
<212> PRT
<213> Homo sapiens

<400> 165

Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser
20 25 30

Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu
35 40 45

Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile
50 55 60

Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr
65 70 75 80

Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser
85 90 95

Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr
100 105 110

His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys
115 120 125

Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg
130 135 140

Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His
145 150 155 160

Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe
165 170 175

Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala His Lys Ser Glu
180 185 190

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
195 200 205

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
210 215 220

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
225 230 235 240

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
245 250 255

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
260 265 270

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
275 280 285

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
290 295 300

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
305 310 315 320

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
325 330 335

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
340 345 350

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
355 360 365

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
370 375 380

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
385 390 395 400

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
405 410 415

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
420 425 430

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
435 440 445

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
450 455 460

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
465 470 475 480

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
485 490 495

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
500 505 510

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
515 520 525

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
530 535 540

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
545 550 555 560

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
565 570 575

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
580 585 590

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
595 600 605

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
610 615 620

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
625 630 635 640

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser

645 650 655

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
660 665 670

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
675 680 685

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
690 695 700

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
705 710 715 720

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
725 730 735

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
740 745 750

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
755 760 765

Leu Gly Leu
770

<210> 166
<211> 771
<212> PRT
<213> Homo sapiens

<400> 166
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser
20 25 30

Ser Asn Phe Gln Ser Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu
35 40 45

Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile
50 55 60

Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr
65 70 75 80

Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser
85 90 95

Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr
100 105 110

His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys
115 120 125

Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg
130 135 140

Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His

```
145                 150                 155                 160

Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe
                165                 170                 175

Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala His Lys Ser Glu
            180                 185                 190

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
        195                 200                 205

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
    210                 215                 220

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
225                 230                 235                 240

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
                245                 250                 255

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
            260                 265                 270

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
        275                 280                 285

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
    290                 295                 300

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
305                 310                 315                 320

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
                325                 330                 335

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
            340                 345                 350

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
        355                 360                 365

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
    370                 375                 380

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
385                 390                 395                 400

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
                405                 410                 415

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
            420                 425                 430

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
        435                 440                 445

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
    450                 455                 460

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
465                 470                 475                 480
```

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
485 490 495

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
500 505 510

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
515 520 525

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
530 535 540

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
545 550 555 560

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
565 570 575

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
580 585 590

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
595 600 605

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
610 615 620

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
625 630 635 640

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
645 650 655

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
660 665 670

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
675 680 685

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
690 695 700

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
705 710 715 720

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
725 730 735

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
740 745 750

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
755 760 765

Leu Gly Leu
770

<210> 167
<211> 769

<212> PRT
<213> Homo sapiens

<400> 167

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ala Gly Val
1               5                   10                  15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
            20                  25                  30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
        35                  40                  45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
    50                  55                  60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65                  70                  75                  80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
                85                  90                  95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
            100                 105                 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
        115                 120                 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
    130                 135                 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145                 150                 155                 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
                165                 170                 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
            180                 185                 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
        195                 200                 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
    210                 215                 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225                 230                 235                 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
                245                 250                 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
            260                 265                 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
        275                 280                 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
    290                 295                 300
```

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305 310 315 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
325 330 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
340 345 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
355 360 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
370 375 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385 390 395 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
405 410 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
420 425 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
435 440 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
450 455 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465 470 475 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
485 490 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
500 505 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
515 520 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
530 535 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545 550 555 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
565 570 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
580 585 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Met Ser Tyr Asn Leu
595 600 605

Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu
610 615 620

Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn

625 630 635 640

Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu
645 650 655

Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile
660 665 670

Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu
675 680 685

Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val
690 695 700

Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met
705 710 715 720

Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu
725 730 735

Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu
740 745 750

Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg
755 760 765

Asn

<210> 168
<211> 769
<212> PRT
<213> Homo sapiens

<400> 168
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Gly Val
1 5 10 15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
20 25 30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
35 40 45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
50 55 60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65 70 75 80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
85 90 95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
100 105 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
115 120 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
130 135 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145 150 155 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
165 170 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
180 185 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
195 200 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
210 215 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225 230 235 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
245 250 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
260 265 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
275 280 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
290 295 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305 310 315 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
325 330 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
340 345 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
355 360 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
370 375 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385 390 395 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
405 410 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
420 425 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
435 440 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
450 455 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465 470 475 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
485 490 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
500 505 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
515 520 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
530 535 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545 550 555 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
565 570 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
580 585 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Met Ser Tyr Asn Leu
595 600 605

Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu
610 615 620

Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn
625 630 635 640

Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu
645 650 655

Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile
660 665 670

Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu
675 680 685

Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val
690 695 700

Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met
705 710 715 720

Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu
725 730 735

Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu
740 745 750

Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg
755 760 765

Asn

<210> 169

<211> 769
<212> PRT
<213> Homo sapiens

<400> 169
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
1 5 10 15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
20 25 30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
35 40 45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
50 55 60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65 70 75 80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
85 90 95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
100 105 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
115 120 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
130 135 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145 150 155 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
165 170 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
180 185 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
195 200 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
210 215 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225 230 235 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
245 250 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
260 265 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
275 280 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
290 295 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305 310 315 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
325 330 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
340 345 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
355 360 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
370 375 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385 390 395 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
405 410 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
420 425 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
435 440 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
450 455 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465 470 475 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
485 490 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
500 505 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
515 520 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
530 535 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545 550 555 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
565 570 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
580 585 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Met Ser Tyr Asn Leu
595 600 605

Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu
610 615 620

```
Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn
625                 630                 635                 640

Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu
                645                 650                 655

Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile
            660                 665                 670

Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu
        675                 680                 685

Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val
    690                 695                 700

Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met
705                 710                 715                 720

Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu
                725                 730                 735

Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu
            740                 745                 750

Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg
        755                 760                 765

Asn


<210> 170
<211> 774
<212> PRT
<213> Homo sapiens

<400> 170
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
```

130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met
705 710 715 720

Asn Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr
725 730 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Arg Leu Arg Arg Lys Glu
770

<210> 171
<211> 774
<212> PRT
<213> Homo sapiens

<400> 171
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu

610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ser Cys Val Met Gln Glu Val Gly Val Ile Glu Ser Pro Leu Met
705 710 715 720

Tyr Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
725 730 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Ser Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Ile Asn Leu Gln Lys
755 760 765

Arg Leu Lys Ser Lys Glu
770

<210> 172
<211> 774
<212> PRT
<213> Homo sapiens

<400> 172
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln

115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Met
690 695 700

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
705 710 715 720

Asn Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr
725 730 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Lys Ile Phe Gln Glu
755 760 765

Arg Leu Arg Arg Lys Glu
770

<210> 173
<211> 774
<212> PRT
<213> Homo sapiens

<400> 173
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly

595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp
675 680 685

Leu Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met
705 710 715 720

Asn Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr
725 730 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Arg Leu Arg Arg Lys Glu
770

<210> 174
<211> 774
<212> PRT
<213> Homo sapiens

<400> 174
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala

100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met
705 710 715 720

Asn Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr
725 730 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Arg Leu Arg Arg Lys Glu
770

<210> 175
<211> 742
<212> PRT
<213> Homo sapiens

<400> 175
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ala Pro Thr Ser Ser Ser Thr Lys
20 25 30

Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile
35 40 45

Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu
50 55 60

Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu
65 70 75 80

Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu
85 90 95

Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn
100 105 110

Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met
115 120 125

Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg
130 135 140

Trp Ile Thr Phe Ser Gln Ser Ile Ile Ser Thr Leu Thr Asp Ala His
145 150 155 160

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
165 170 175

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
180 185 190

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
195 200 205

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
210 215 220

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
225 230 235 240

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
245 250 255

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
260 265 270

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
275 280 285

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
290 295 300

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
305 310 315 320

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
325 330 335

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
340 345 350

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
355 360 365

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
370 375 380

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
385 390 395 400

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
405 410 415

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
420 425 430

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
435 440 445

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
450 455 460

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
465 470 475 480

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
485 490 495

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
500 505 510

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
515 520 525

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
530 535 540

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
545 550 555 560

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
565 570 575

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser

580 585 590

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
595 600 605

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
610 615 620

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
625 630 635 640

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
645 650 655

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
660 665 670

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
675 680 685

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
690 695 700

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
705 710 715 720

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
725 730 735

Gln Ala Ala Leu Gly Leu
740

<210> 176
<211> 742
<212> PRT
<213> Homo sapiens

<400> 176
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln

115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu
610 615 620

His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr
625 630 635 640

Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro
645 650 655

Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu
660 665 670

Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His
675 680 685

Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu
690 695 700

Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr
705 710 715 720

Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Ser Gln Ser
725 730 735

Ile Ile Ser Thr Leu Thr
740

<210> 177
<211> 742

<212> PRT
<213> Homo sapiens

<400> 177

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ala Pro Thr Ser Ser Ser Thr Lys
            20                  25                  30

Lys Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile
        35                  40                  45

Leu Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu
    50                  55                  60

Thr Phe Lys Phe Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu
65                  70                  75                  80

Gln Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu
                85                  90                  95

Ala Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn
            100                 105                 110

Ile Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met
        115                 120                 125

Cys Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg
    130                 135                 140

Trp Ile Thr Phe Cys Gln Ser Ile Ile Ser Thr Leu Thr Asp Ala His
145                 150                 155                 160

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
                165                 170                 175

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
            180                 185                 190

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
        195                 200                 205

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
    210                 215                 220

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
225                 230                 235                 240

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
                245                 250                 255

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
            260                 265                 270

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
        275                 280                 285

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
    290                 295                 300
```

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
305   310   315   320

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
                325   330   335

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
            340   345   350

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
        355   360   365

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
    370   375   380

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
385   390   395   400

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
                405   410   415

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
            420   425   430

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
        435   440   445

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
    450   455   460

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
465   470   475   480

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
                485   490   495

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
            500   505   510

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
        515   520   525

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
    530   535   540

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
545   550   555   560

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
                565   570   575

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
            580   585   590

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
        595   600   605

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
    610   615   620

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn

625 630 635 640

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
645 650 655

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
660 665 670

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
675 680 685

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
690 695 700

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
705 710 715 720

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
725 730 735

Gln Ala Ala Leu Gly Leu
740

<210> 178
<211> 742
<212> PRT
<213> Homo sapiens

<400> 178
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro

165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

```
Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu
    610                 615                 620

His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr
625                 630                 635                 640

Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro
                645                 650                 655

Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu
            660                 665                 670

Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His
        675                 680                 685

Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu
    690                 695                 700

Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr
705                 710                 715                 720

Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser
                725                 730                 735

Ile Ile Ser Thr Leu Thr
            740


<210> 179
<211> 738
<212> PRT
<213> Homo sapiens

<400> 179
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                   10                  15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
            20                  25                  30
```

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
35 40 45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
50 55 60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65 70 75 80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
85 90 95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
100 105 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
115 120 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
130 135 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr Asp Ala His Lys Ser Glu Val
145 150 155 160

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
165 170 175

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
180 185 190

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
195 200 205

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
210 215 220

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
225 230 235 240

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
245 250 255

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
260 265 270

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
275 280 285

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
290 295 300

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
305 310 315 320

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
325 330 335

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
340 345 350

```
Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
        355                 360                 365

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
    370                 375                 380

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
385                 390                 395                 400

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
                405                 410                 415

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
            420                 425                 430

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
        435                 440                 445

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
    450                 455                 460

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
465                 470                 475                 480

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
                485                 490                 495

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
            500                 505                 510

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
        515                 520                 525

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
    530                 535                 540

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
545                 550                 555                 560

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
                565                 570                 575

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
            580                 585                 590

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
        595                 600                 605

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
    610                 615                 620

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
625                 630                 635                 640

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
                645                 650                 655

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
            660                 665                 670

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
```

```
        675                 680                 685

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
    690                 695                 700

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
705                 710                 715                 720

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
                725                 730                 735

Gly Leu


<210> 180
<211> 738
<212> PRT
<213> Homo sapiens

<400> 180
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                   10                  15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
            20                  25                  30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
        35                  40                  45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
    50                  55                  60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65                  70                  75                  80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
                85                  90                  95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
            100                 105                 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
        115                 120                 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
    130                 135                 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr Asp Ala His Lys Ser Glu Val
145                 150                 155                 160

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
                165                 170                 175

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
            180                 185                 190

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
        195                 200                 205

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
    210                 215                 220
```

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
225 230 235 240

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
245 250 255

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
260 265 270

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
275 280 285

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
290 295 300

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
305 310 315 320

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
325 330 335

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
340 345 350

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
355 360 365

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
370 375 380

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
385 390 395 400

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
405 410 415

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
420 425 430

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
435 440 445

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
450 455 460

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
465 470 475 480

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
485 490 495

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
500 505 510

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
515 520 525

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
530 535 540

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
545 550 555 560

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
565 570 575

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
580 585 590

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
595 600 605

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
610 615 620

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
625 630 635 640

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
645 650 655

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
660 665 670

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
675 680 685

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
690 695 700

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
705 710 715 720

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
725 730 735

Gly Leu

<210> 181
<211> 165
<212> PRT
<213> Homo sapiens

<400> 181
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu

```
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165

<210> 182
<211> 165
<212> PRT
<213> Homo sapiens

<400> 182
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                  10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165

<210> 183
<211> 165
<212> PRT
<213> Homo sapiens
```

<400> 183
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1   5   10   15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160

Leu Arg Ser Lys Glu
                165

<210> 184
<211> 165
<212> PRT
<213> Homo sapiens

<400> 184
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1   5   10   15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys

```
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210> 185
<211> 165
<212> PRT
<213> Homo sapiens

<400> 185
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                  10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165

<210> 186
<211> 165
<212> PRT
<213> Homo sapiens

<400> 186
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
```

```
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210> 187
<211> 165
<212> PRT
<213> Homo sapiens

<400> 187
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
```

```
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210> 188
<211> 165
<212> PRT
<213> Homo sapiens

<400> 188
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210> 189
<211> 165
<212> PRT
<213> Homo sapiens

<400> 189
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15
```

```
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210> 190
<211> 165
<212> PRT
<213> Homo sapiens

<400> 190
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125
```

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 191
<211> 166
<212> PRT
<213> Homo sapiens

<400> 191
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn
165

<210> 192
<211> 166
<212> PRT
<213> Homo sapiens

<400> 192
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn
165

<210> 193
<211> 187
<212> PRT
<213> Homo sapiens

<400> 193
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
35 40 45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
50 55 60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65 70 75 80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
85 90 95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
100 105 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
115 120 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
130 135 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145 150 155 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
165 170 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn
180 185

<210> 194
<211> 166
<212> PRT
<213> Homo sapiens

<400> 194
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn
165

<210> 195
<211> 187
<212> PRT
<213> Homo sapiens

<400> 195
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg

20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
35 40 45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
50 55 60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65 70 75 80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
85 90 95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
100 105 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
115 120 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
130 135 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145 150 155 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
165 170 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn
180 185

<210> 196
<211> 166
<212> PRT
<213> Homo sapiens

<400> 196
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg

115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn
165

<210> 197
<211> 187
<212> PRT
<213> Homo sapiens

<400> 197
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
35 40 45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
50 55 60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65 70 75 80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
85 90 95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
100 105 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
115 120 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
130 135 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145 150 155 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
165 170 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn
180 185

<210> 198
<211> 187
<212> PRT
<213> Homo sapiens

<400> 198

Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
35 40 45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
50 55 60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65 70 75 80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
85 90 95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
100 105 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
115 120 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
130 135 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145 150 155 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
165 170 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn
180 185

<210> 199
<211> 166
<212> PRT
<213> Homo sapiens

<400> 199
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

```
His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
            100                 105                 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
        115                 120                 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
    130                 135                 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160

Thr Gly Tyr Leu Arg Asn
                165


&lt;210&gt; 200
&lt;211&gt; 166
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 200
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
  1               5                  10                  15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
            20                  25                  30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
        35                  40                  45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
    50                  55                  60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
 65                  70                  75                  80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
                 85                  90                  95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
            100                 105                 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
        115                 120                 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
    130                 135                 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160

Thr Gly Tyr Leu Arg Asn
                165


&lt;210&gt; 201
&lt;211&gt; 166
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens
```

<400> 201
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn
165

<210> 202
<211> 165
<212> PRT
<213> Homo sapiens

<400> 202
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
100 105 110

Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 203
<211> 165
<212> PRT
<213> Homo sapiens

<400> 203
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ser Cys Val Met Gln Glu Val Gly Val Ile Glu Ser Pro Leu Met Tyr
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Ser Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Ile Asn Leu Gln Lys Arg
145 150 155 160

Leu Lys Ser Lys Glu
165

<210> 204
<211> 165
<212> PRT
<213> Homo sapiens

<400> 204
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met

```
 1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Met Glu
                85                  90                  95

Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met Asn
            100                 105                 110

Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Lys Ile Phe Gln Glu Arg
145                 150                 155                 160

Leu Arg Arg Lys Glu
                165


<210> 205
<211> 165
<212> PRT
<213> Homo sapiens

<400> 205
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp Leu
65                  70                  75                  80

Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
            100                 105                 110

Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
```

115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 206
<211> 165
<212> PRT
<213> Homo sapiens

<400> 206
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
100 105 110

Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 207
<211> 153
<212> PRT
<213> Homo sapiens

<400> 207
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

```
Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
                20                  25                  30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
            35                  40                  45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
    50                  55                  60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65                  70                  75                  80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
                85                  90                  95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
            100                 105                 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
        115                 120                 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
    130                 135                 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr
145                 150


<210> 208
<211> 153
<212> PRT
<213> Homo sapiens

<400> 208
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                   10                  15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
            20                  25                  30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
        35                  40                  45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
    50                  55                  60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65                  70                  75                  80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
                85                  90                  95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
            100                 105                 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
        115                 120                 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
    130                 135                 140
```

Cys Gln Ser Ile Ile Ser Thr Leu Thr
145 150

<210> 209
<211> 153
<212> PRT
<213> Homo sapiens

<400> 209
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
20 25 30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
35 40 45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
50 55 60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65 70 75 80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
85 90 95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
100 105 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
115 120 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
130 135 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr
145 150

<210> 210
<211> 153
<212> PRT
<213> Homo sapiens

<400> 210
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
20 25 30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
35 40 45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
50 55 60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65 70 75 80

```
Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
                85                  90                  95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
            100                 105                 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
        115                 120                 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
    130                 135                 140

Cys Gln Ser Ile Ile Ser Thr Leu Thr
145                 150


<210> 211
<211> 153
<212> PRT
<213> Homo sapiens

<400> 211
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                   10                  15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
            20                  25                  30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
        35                  40                  45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
    50                  55                  60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65                  70                  75                  80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
                85                  90                  95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
            100                 105                 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
        115                 120                 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
    130                 135                 140

Ser Gln Ser Ile Ile Ser Thr Leu Thr
145                 150


<210> 212
<211> 153
<212> PRT
<213> Homo sapiens

<400> 212
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
```

1 5 10 15

Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu
20 25 30

Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile
35 40 45

Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe
50 55 60

Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu
65 70 75 80

Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys
85 90 95

Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile
100 105 110

Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala
115 120 125

Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe
130 135 140

Ser Gln Ser Ile Ile Ser Thr Leu Thr
145 150

<210> 213
<211> 20
<212> DNA
<213> Homo sapiens

<400> 213
catacaaact taagagtcca 20

<210> 214
<211> 56
<212> DNA
<213> Homo sapiens

<400> 214
ctttaaatcg atgagcaacc tcactcttgt gtgcatcagc gttagccaaa gaagca 56

<210> 215
<211> 20
<212> DNA
<213> Homo sapiens

<400> 215
catacaaact taagagtcca 20

<210> 216
<211> 56
<212> DNA
<213> Homo sapiens

<400> 216
ctttaaatcg atgagcaacc tcactcttgt gtgcatctgc cgatattttg gctgca 56

<210> 217
<211> 20
<212> DNA
<213> Homo sapiens

<400> 217
catacaaact taagagtcca 20

<210> 218
<211> 56
<212> DNA
<213> Homo sapiens

<400> 218
ctttaaatcg atgagcaacc tcactcttgt gtgcatctct cttatccaaa gaacct 56

<210> 219
<211> 41
<212> DNA
<213> Homo sapiens

<400> 219
cgcgcgcgtc gacaaaagat gtgatctgcc tcaaacccac a 41

<210> 220
<211> 59
<212> DNA
<213> Homo sapiens

<400> 220
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 221
<211> 27
<212> DNA
<213> Homo sapiens

<400> 221
gttagcagag tagcagggct ttcggct 27

<210> 222
<211> 59
<212> DNA
<213> Homo sapiens

<400> 222
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 223
<211> 41
<212> DNA
<213> Homo sapiens

<400> 223
cgcgcgcgtc gacaaaagat gtgatctgcc tcaaacccac a 41

<210> 224
<211> 59
<212> DNA
<213> Homo sapiens

<400> 224
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 225
<211> 38
<212> DNA
<213> Homo sapiens

<400> 225
caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 226
<211> 39
<212> DNA
<213> Homo sapiens

<400> 226
gaattcggcg cgccttattc cttacttctt aaactttct 39

<210> 227
<211> 107
<212> DNA
<213> Homo sapiens

<400> 227
gcgcgcggat ccgccaccat ggccttgacc tttgctttac tggtggccct cctggtgctc 60
agctgcaagt caagctgctc tgtgggctgt gatctgcctc aaaccca 107

<210> 228
<211> 59
<212> DNA
<213> Homo sapiens

<400> 228
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 229
<211> 25
<212> DNA
<213> Homo sapiens

<400> 229
gcatgtgatc tgcctcaaac ccaca 25

<210> 230
<211> 59
<212> DNA
<213> Homo sapiens

<400> 230
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 231
<211> 40
<212> DNA
<213> Homo sapiens

<400> 231
cgcgcgcgtc gacaaaagaa tgagctacaa cttgcttgga 40

<210> 232
<211> 55
<212> DNA
<213> Homo sapiens

<400> 232
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcgtt tcggaggtaa cctgt 55

<210> 233
<211> 106
<212> DNA
<213> Homo sapiens

<400> 233
gcgcggatcc gaattccgcc gccatgacca acaagtgtct cctccaaatt gctctcctgt 60
tgtgcttctc cactacagct ctttccatga gctacaactt gcttgg 106

<210> 234
<211> 55
<212> DNA
<213> Homo sapiens

<400> 234
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcgtt tcggaggtaa cctgt 55

<210> 235
<211> 38
<212> DNA
<213> Homo sapiens

<400> 235
caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 236
<211> 39
<212> DNA
<213> Homo sapiens

<400> 236
gcgcatggcg cgccttattc cttcctcctt aatctttct 39

<210> 237
<211> 38
<212> DNA
<213> Homo sapiens

<400> 237
caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 238
<211> 38
<212> DNA
<213> Homo sapiens

<400> 238
gcgcatggcg cgcctcattc cttactcttc aatctttt 38

<210> 239
<211> 38
<212> DNA
<213> Homo sapiens

<400> 239
caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 240
<211> 39
<212> DNA
<213> Homo sapiens

<400> 240
gcgcatggcg cgccttattc cttcctcctt aatctttct 39

<210> 241
<211> 38
<212> DNA
<213> Homo sapiens

<400> 241
caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 242
<211> 39
<212> DNA
<213> Homo sapiens

<400> 242
gcgcatggcg cgccttattc cttcctcctt aatctttct 39

<210> 243
<211> 21
<212> DNA
<213> Homo sapiens

<400> 243
agaagtgctg caaggctgac g 21

<210> 244
<211> 20
<212> DNA
<213> Homo sapiens

<400> 244
acctgaccta caggaaagag 20

<210> 245
<211> 2418
<212> DNA
<213> Homo sapiens

<400> 245
atgaacattt tctacatttt cttgttcttg ttgtctttcg ttcaaggttt ggaacacact 60
cacagaagag gttctttgga taagagagat gcacacaaga gtgaggttgc tcatcgattt 120
aaagatttgg gagaagaaaa tttcaaagcc ttggtgttga ttgcctttgc tcagtatctt 180
cagcagtgtc catttgaaga tcatgtaaaa ttagtgaatg aagtaactga atttgcaaaa 240
acatgtgttg ctgatgagtc agctgaaaat tgtgacaaat cacttcatac cctttttgga 300
gacaaattat gcacagttgc aactcttcgt gaaacctatg gtgaaatggc tgactgctgt 360
gcaaaacaag aacctgagag aaatgaatgc ttcttgcaac acaaagatga caacccaaac 420
ctcccccgat tggtgagacc agaggttgat gtgatgtgca ctgcttttca tgacaatgaa 480
gagacatttt tgaaaaaata cttatatgaa attgccagaa gacatcctta cttttatgcc 540
ccggaactcc ttttctttgc taaaaggtat aaagctgctt ttacagaatg ttgccaagct 600
gctgataaag ctgcctgcct gttgccaaag ctcgatgaac ttcgggatga agggaaggct 660
tcgtctgcca aacagagact caagtgtgcc agtctccaaa aatttggaga aagagctttc 720
aaagcatggg cagtagctcg cctgagccag agatttccca aagctgagtt tgcagaagtt 780
tccaagttag tgacagatct taccaaagtc cacacggaat gctgccatgg agatctgctt 840
gaatgtgctg atgacagggc ggaccttgcc aagtatatct gtgaaaatca agattcgatc 900
tccagtaaac tgaaggaatg ctgtgaaaaa cctctgttgg aaaaatccca ctgcattgcc 960
gaagtggaaa atgatgagat gcctgctgac ttgccttcat tagctgctga ttttgttgaa 1020
agtaaggatg tttgcaaaaa ctatgctgag gcaaaggatg tcttcctggg catgtttttg 1080
tatgaatatg caagaaggca tcctgattac tctgtcgtgc tgctgctgag acttgccaag 1140
acatatgaaa ccactctaga gaagtgctgt gccgctgcag atcctcatga atgctatgcc 1200
aaagtgttcg atgaatttaa acctcttgtg gaagagcctc agaatttaat caaacaaaat 1260
tgtgagcttt ttgagcagct tggagagtac aaattccaga atgcgctatt agttcgttac 1320
accaagaaag taccccaagt gtcaactcca actcttgtag aggtctcaag aaacctagga 1380
aaagtgggca gcaaatgttg taaacatcct gaagcaaaaa gaatgccctg tgcagaagac 1440
tatctatccg tggtcctgaa ccagttatgt gtgttgcatg agaaaacgcc agtaagtgac 1500
agagtcacca aatgctgcac agaatccttg gtgaacaggc gaccatgctt ttcagctctg 1560
gaagtcgatg aaacatacgt tcccaaagag tttaatgctg aaacattcac cttccatgca 1620
gatatatgca cactttctga gaaggagaga caaatcaaga aacaaactgc acttgttgag 1680
ctcgtgaaac acaagcccaa ggcaacaaaa gagcaactga aagctgttat ggatgatttc 1740
gcagcttttg tagagaagtg ctgcaaggct gacgataagg agacctgctt tgccgaggag 1800
ggtaaaaaac ttgttgctgc aagtcaagct gccttaggct tattcccaac aattccctta 1860
tccaggcttt ttgacaacgc tatgctccgc gcccatcgtc tgcaccagct ggcctttgac 1920
acctaccagg agtttgaaga agcctatatc ccaaaggaac agaagtattc attcctgcag 1980
aacccccaga cctccctctg tttctcagag tctattccga caccctccaa cagggaggaa 2040
acacaacaga aatccaacct agagctgctc cgcatctccc tgctgctcat ccagtcgtgg 2100
ctggagcccg tgcagttcct caggagtgtc ttcgccaaca gcctggtgta cggcgcctct 2160
gacagcaacg tctatgacct cctaaaggac ctagaggaag gcatccaaac gctgatgggg 2220
aggctggaag atggcagccc ccggactggg cagatcttca agcagaccta cagcaagttc 2280
gacacaaact cacacaacga tgacgcacta ctcaagaact acgggctgct ctactgcttc 2340
aggaaggaca tggacaaggt cgagacattc ctgcgcatcg tgcagtgccg ctctgtggag 2400
ggatcctgtg gcttctaa 2418

<210> 246
<211> 2388
<212> DNA
<213> Homo sapiens

<400> 246
atgcttttgc aagctttcct tttccttttg gctggttttg cagccaaaat atcggcagat 60
gcacacaaga gtgaggttgc tcatcgattt aaagatttgg gagaagaaaa tttcaaagcc 120
ttggtgttga ttgcctttgc tcagtatctt cagcagtgtc catttgaaga tcatgtaaaa 180
ttagtgaatg aagtaactga atttgcaaaa acatgtgttg ctgatgagtc agctgaaaat 240
tgtgacaaat cacttcatac cctttttgga gacaaattat gcacagttgc aactcttcgt 300

```
gaaacctatg gtgaaatggc tgactgctgt gcaaaacaag aacctgagag aaatgaatgc    360
ttcttgcaac acaaagatga caacccaaac ctccccgat tggtgagacc agaggttgat     420
gtgatgtgca ctgcttttca tgacaatgaa gagacatttt tgaaaaaata cttatatgaa    480
attgccagaa gacatcctta cttttatgcc ccggaactcc ttttctttgc taaaaggtat    540
aaagctgctt ttacagaatg ttgccaagct gctgataaag ctgcctgcct gttgccaaag    600
ctcgatgaac ttcgggatga agggaaggct tcgtctgcca aacagagact caagtgtgcc    660
agtctccaaa aatttggaga aagagctttc aaagcatggg cagtagctcg cctgagccag    720
agatttccca aagctgagtt tgcagaagtt tccaagttag tgacagatct taccaaagtc    780
cacacggaat gctgccatgg agatctgctt gaatgtgctg atgacagggc ggaccttgcc    840
aagtatatct gtgaaaatca agattcgatc tccagtaaac tgaaggaatg ctgtgaaaaa    900
cctctgttgg aaaaatccca ctgcattgcc gaagtggaaa atgatgagat gcctgctgac    960
ttgccttcat tagctgctga ttttgttgaa agtaaggatg tttgcaaaaa ctatgctgag   1020
gcaaaggatg tcttcctggg catgtttttg tatgaatatg caagaaggca tcctgattac   1080
tctgtcgtgc tgctgctgag acttgccaag acatatgaaa ccactctaga gaagtgctgt   1140
gccgctgcag atcctcatga atgctatgcc aaagtgttcg atgaatttaa acctcttgtg   1200
gaagagcctc agaatttaat caaacaaaat tgtgagcttt ttgagcagct tggagagtac   1260
aaattccaga atgcgctatt agttcgttac accaagaaag taccccaagt gtcaactcca   1320
actcttgtag aggtctcaag aaacctagga aaagtgggca gcaaatgttg taaacatcct   1380
gaagcaaaaa gaatgccctg tgcagaagac tatctatccg tggtcctgaa ccagttatgt   1440
gtgttgcatg agaaaacgcc agtaagtgac agagtcacca aatgctgcac agaatccttg   1500
gtgaacaggc gaccatgctt ttcagctctg gaagtcgatg aaacatacgt tcccaaagag   1560
tttaatgctg aaacattcac cttccatgca gatatatgca cactttctga gaaggagaga   1620
caaatcaaga aacaaactgc acttgttgag ctcgtgaaac acaagcccaa ggcaacaaaa   1680
gagcaactga aagctgttat ggatgatttc gcagcttttg tagagaagtg ctgcaaggct   1740
gacgataagg agacctgctt tgccgaggag ggtaaaaaac ttgttgctgc aagtcaagct   1800
gccttaggct tattcccaac aattccctta tccaggcttt ttgacaacgc tatgctccgc   1860
gcccatcgtc tgcaccagct ggcctttgac acctaccagg agtttgaaga agcctatatc   1920
ccaaaggaac agaagtattc attcctgcag aacccccaga cctccctctg tttctcagag   1980
tctattccga caccctccaa cagggaggaa acacaacaga aatccaacct agagctgctc   2040
cgcatctccc tgctgctcat ccagtcgtgg ctggagcccg tgcagttcct caggagtgtc   2100
ttcgccaaca gcctggtgta cggcgcctct gacagcaacg tctatgacct cctaaaggac   2160
ctagaggaag gcatccaaac gctgatgggg aggctggaag atggcagccc ccggactggg   2220
cagatcttca agcagaccta cagcaagttc gacacaaact cacacaacga tgacgcacta   2280
ctcaagaact acgggctgct ctactgcttc aggaaggaca tggacaaggt cgagacattc   2340
ctgcgcatcg tgcagtgccg ctctgtggag ggatcctgtg gcttctaa                2388
```

<210> 247
<211> 2382
<212> DNA
<213> Homo sapiens

<400> 247

```
atgttcaagt ctgttgttta ctctattttg gctgcttctt tggctaacgc tgatgcacac     60
aagagtgagg ttgctcatcg atttaaagat ttgggagaag aaaatttcaa agccttggtg    120
ttgattgcct ttgctcagta tcttcagcag tgtccatttg aagatcatgt aaaattagtg    180
aatgaagtaa ctgaatttgc aaaaacatgt gttgctgatg agtcagctga aaattgtgac    240
aaatcacttc ataccctttt tggagacaaa ttatgcacag ttgcaactct tcgtgaaacc    300
tatggtgaaa tggctgactg ctgtgcaaaa caagaacctg agagaaatga atgcttcttg    360
caacacaaag atgacaaccc aaacctcccc cgattggtga gaccagaggt tgatgtgatg    420
tgcactgctt ttcatgacaa tgaagagaca tttttgaaaa aatacttata tgaaattgcc    480
agaagacatc cttactttta tgccccggaa ctccttttct ttgctaaaag gtataaagct    540
gcttttacag aatgttgcca agctgctgat aaagctgcct gcctgttgcc aaagctcgat    600
gaacttcggg atgaagggaa ggcttcgtct gccaaacaga gactcaagtg tgccagtctc    660
caaaaatttg gagaaagagc tttcaaagca tgggcagtag ctcgcctgag ccagagattt    720
cccaaagctg agtttgcaga agtttccaag ttagtgacag atcttaccaa agtccacacg    780
gaatgctgcc atggagatct gcttgaatgt gctgatgaca gggcggacct tgccaagtat    840
atctgtgaaa atcaagattc gatctccagt aaactgaagg aatgctgtga aaaacctctg    900
ttggaaaaat cccactgcat tgccgaagtg gaaaatgatg agatgcctgc tgacttgcct    960
tcattagctg ctgattttgt tgaaagtaag gatgtttgca aaaactatgc tgaggcaaag   1020
gatgtcttcc tgggcatgtt tttgtatgaa tatgcaagaa ggcatcctga ttactctgtc   1080
gtgctgctgc tgagacttgc caagacatat gaaaccactc tagagaagtg ctgtgccgct   1140
```

gcagatcctc atgaatgcta tgccaaagtg ttcgatgaat ttaaacctct tgtggaagag 1200
cctcagaatt taatcaaaca aaattgtgag ctttttgagc agcttggaga gtacaaattc 1260
cagaatgcgc tattagttcg ttacaccaag aaagtacccc aagtgtcaac tccaactctt 1320
gtagaggtct caagaaacct aggaaaagtg ggcagcaaat gttgtaaaca tcctgaagca 1380
aaaagaatgc cctgtgcaga agactatcta tccgtggtcc tgaaccagtt atgtgtgttg 1440
catgagaaaa cgccagtaag tgacagagtc accaaatgct gcacagaatc cttggtgaac 1500
aggcgaccat gcttttcagc tctggaagtc gatgaaacat acgttcccaa agagtttaat 1560
gctgaaacat tcaccttcca tgcagatata tgcacacttt ctgagaagga gagacaaatc 1620
aagaaacaaa ctgcacttgt tgagctcgtg aaacacaagc ccaaggcaac aaaagagcaa 1680
ctgaaagctg ttatggatga tttcgcagct tttgtagaga agtgctgcaa ggctgacgat 1740
aaggagacct gctttgccga ggagggtaaa aaacttgttg ctgcaagtca agctgcctta 1800
ggcttattcc caacaattcc cttatccagg ctttttgaca acgctatgct ccgcgcccat 1860
cgtctgcacc agctggcctt tgacacctac caggagtttg aagaagccta tatcccaaag 1920
gaacagaagt attcattcct gcagaacccc cagacctccc tctgtttctc agagtctatt 1980
ccgacaccct ccaacaggga ggaaacacaa cagaaatcca acctagagct gctccgcatc 2040
tccctgctgc tcatccagtc gtggctggag cccgtgcagt tcctcaggag tgtcttcgcc 2100
aacagcctgg tgtacggcgc ctctgacagc aacgtctatg acctcctaaa ggacctagag 2160
gaaggcatcc aaacgctgat ggggaggctg gaagatggca gcccccggac tgggcagatc 2220
ttcaagcaga cctacagcaa gttcgacaca aactcacaca acgatgacgc actactcaag 2280
aactacgggc tgctctactg cttcaggaag gacatggaca aggtcgagac attcctgcgc 2340
atcgtgcagt gccgctctgt ggagggatcc tgtggcttct aa 2382

<210> 248
<211> 2403
<212> DNA
<213> Homo sapiens

<400> 248
atgaagtggg taagctttat ttcccttctt tttctcttta gctcggctta ttccggttct 60
ttggataaga gagatgcaca caagagtgag gttgctcatc gatttaaaga tttgggagaa 120
gaaaatttca aagccttggt gttgattgcc tttgctcagt atcttcagca gtgtccattt 180
gaagatcatg taaaattagt gaatgaagta actgaatttg caaaaacatg tgttgctgat 240
gagtcagctg aaaattgtga caaatcactt cataccctttt ttggagacaa attatgcaca 300
gttgcaactc ttcgtgaaac ctatggtgaa atggctgact gctgtgcaaa acaagaacct 360
gagagaaatg aatgcttctt gcaacacaaa gatgacaacc caaacctccc ccgattggtg 420
agaccagagg ttgatgtgat gtgcactgct tttcatgaca atgaagagac atttttgaaa 480
aaatacttat atgaaattgc cagaagacat ccttactttt atgccccgga actccttttc 540
tttgctaaaa ggtataaagc tgcttttaca gaatgttgcc aagctgctga taaagctgcc 600
tgcctgttgc caaagctcga tgaacttcgg gatgaaggga aggcttcgtc tgccaaacag 660
agactcaagt gtgccagtct ccaaaaattt ggagaaagag ctttcaaagc atgggcagta 720
gctcgcctga gccagagatt tcccaaagct gagtttgcag aagtttccaa gttagtgaca 780
gatcttacca aagtccacac ggaatgctgc catggagatc tgcttgaatg tgctgatgac 840
agggcggacc ttgccaagta tatctgtgaa aatcaagatt cgatctccag taaactgaag 900
gaatgctgtg aaaaacctct gttggaaaaa tcccactgca ttgccgaagt ggaaaatgat 960
gagatgcctg ctgacttgcc ttcattagct gctgattttg ttgaaagtaa ggatgtttgc 1020
aaaaactatg ctgaggcaaa ggatgtcttc ctgggcatgt ttttgtatga atatgcaaga 1080
aggcatcctg attactctgt cgtgctgctg ctgagacttg ccaagacata tgaaaccact 1140
ctagagaagt gctgtgccgc tgcagatcct catgaatgct atgccaaagt gttcgatgaa 1200
tttaaacctc ttgtggaaga gcctcagaat ttaatcaaac aaaattgtga gctttttgag 1260
cagcttggag agtacaaatt ccagaatgcg ctattagttc gttacaccaa gaaagtaccc 1320
caagtgtcaa ctccaactct tgtagaggtc tcaagaaacc taggaaaagt gggcagcaaa 1380
tgttgtaaac atcctgaagc aaaaagaatg ccctgtgcag aagactatct atccgtggtc 1440
ctgaaccagt tatgtgtgtt gcatgagaaa acgccagtaa gtgacagagt caccaaatgc 1500
tgcacagaat ccttggtgaa caggcgacca tgcttttcag ctctggaagt cgatgaaaca 1560
tacgttccca aagagtttaa tgctgaaaca ttcaccttcc atgcagatat atgcacactt 1620
tctgagaagg agagacaaat caagaaacaa actgcacttg ttgagctcgt gaaacacaag 1680
cccaaggcaa caaaagagca actgaaagct gttatggatg atttcgcagc ttttgtagag 1740
aagtgctgca aggctgacga taaggagacc tgctttgccg aggagggtaa aaaacttgtt 1800
gctgcaagtc aagctgcctt aggcttattc ccaacaattc ccttatccag gctttttgac 1860
aacgctatgc tccgcgccca tcgtctgcac cagctggcct ttgacaccta ccaggagttt 1920
gaagaagcct atatcccaaa ggaacagaag tattcattcc tgcagaaccc ccagacctcc 1980

```
ctctgtttct cagagtctat tccgacaccc tccaacaggg aggaaacaca acagaaatcc   2040
aacctagagc tgctccgcat ctccctgctg ctcatccagt cgtggctgga gcccgtgcag   2100
ttcctcagga gtgtcttcgc caacagcctg gtgtacggcg cctctgacag caacgtctat   2160
gacctcctaa aggacctaga ggaaggcatc caaacgctga tggggaggct ggaagatggc   2220
agcccccgga ctgggcagat cttcaagcag acctacagca agttcgacac aaactcacac   2280
aacgatgacg cactactcaa gaactacggg ctgctctact gcttcaggaa ggacatggac   2340
aaggtcgaga cattcctgcg catcgtgcag tgccgctctg tggagggatc ctgtggcttc   2400
taa                                                                 2403
```

<210> 249
<211> 2325
<212> DNA
<213> Homo sapiens

<400> 249

```
atgaagtggg taagctttat ttcccttctt tttctcttta gctcggctta ttccggttct     60
ttggataaga gagatgcaca caagagtgag gttgctcatc gatttaaaga tttgggagaa    120
gaaaatttca aagccttggt gttgattgcc tttgctcagt atcttcagca gtgtccattt    180
gaagatcatg taaaattagt gaatgaagta actgaatttg caaaaacatg tgttgctgat    240
gagtcagctg aaaattgtga caaatcactt cataccctttt ttggagacaa attatgcaca    300
gttgcaactc ttcgtgaaac ctatggtgaa atggctgact gctgtgcaaa acaagaacct    360
gagagaaatg aatgcttctt gcaacacaaa gatgacaacc caaacctccc ccgattggtg    420
agaccagagg ttgatgtgat gtgcactgct tttcatgaca atgaagagac atttttgaaa    480
aaatacttat atgaaattgc cagaagacat ccttactttt atgccccgga actccttttc    540
tttgctaaaa ggtataaagc tgcttttaca gaatgttgcc aagctgctga taaagctgcc    600
tgcctgttgc caaagctcga tgaacttcgg gatgaaggga aggcttcgtc tgccaaacag    660
agactcaagt gtgccagtct ccaaaaattt ggagaaagag ctttcaaagc atgggcagta    720
gctcgcctga gccagagatt tcccaaagct gagtttgcag aagtttccaa gttagtgaca    780
gatcttacca aagtccacac ggaatgctgc catggagatc tgcttgaatg tgctgatgac    840
agggcggacc ttgccaagta tatctgtgaa aatcaagatt cgatctccag taaactgaag    900
gaatgctgtg aaaaacctct gttggaaaaa tcccactgca ttgccgaagt ggaaaatgat    960
gagatgcctg ctgacttgcc ttcattagct gctgattttg ttgaaagtaa ggatgtttgc   1020
aaaaactatg ctgaggcaaa ggatgtcttc ctgggcatgt ttttgtatga atatgcaaga   1080
aggcatcctg attactctgt cgtgctgctg ctgagacttg ccaagacata tgaaaccact   1140
ctagagaagt gctgtgccgc tgcagatcct catgaatgct atgccaaagt gttcgatgaa   1200
tttaaacctc ttgtggaaga gcctcagaat ttaatcaaac aaaattgtga gctttttgag   1260
cagcttggag agtacaaatt ccagaatgcg ctattagttc gttacaccaa gaaagtaccc   1320
caagtgtcaa ctccaactct tgtagaggtc tcaagaaacc taggaaaagt gggcagcaaa   1380
tgttgtaaac atcctgaagc aaaaagaatg ccctgtgcag aagactatct atccgtggtc   1440
ctgaaccagt tatgtgtgtt gcatgagaaa acgccagtaa gtgacagagt caccaaatgc   1500
tgcacagaat ccttggtgaa caggcgacca tgcttttcag ctctggaagt cgatgaaaca   1560
tacgtyccca aagagtttaa tgctgaaaca ttcaccttcc atgcagatat atgcacactt   1620
tctgagaagg agagacaaat caagaaacaa actgcacttg ttgagctcgt gaaacacaag   1680
cccaaggcaa caaaagagca actgaaagct gttatggatg atttcgcagc ttttgtagag   1740
aagtgctgca aggctgacga taaggagacc tgctttgccg aggagggtaa aaaacttgtt   1800
gctgcaagtc aagctgcctt aggcttatgt gatctgcctc aaacccacag cctgggttct   1860
agaaggacct tgatgctcct ggcacagatg aggagaatct ctcttttctc ctgcttgaag   1920
gacagacatg actttggatt tccccaggag gagtttggca accagttcca aaaggctgaa   1980
accatccctg tcctccatga gatgatccag cagatcttca atctcttcag cacaaaggac   2040
tcatctgctg cttgggatga gaccctccta gacaaattct acactgaact ctaccagcag   2100
ctgaatgacc tggaagcctg tgtgatacag ggggtggggg tgacagagac tcccctgatg   2160
aaggaggact ccattctggc tgtgaggaaa tacttccaaa gaatcactct ctatctgaaa   2220
gagaagaaat acagcccttg tgcctgggag gttgtcagag cagaaatcat gagatctttt   2280
tctttgtcaa caaacttgca agaaagttta agaagtaagg aataa                   2325
```

<210> 250
<211> 357
<212> DNA
<213> Homo sapiens

<400> 250

cactctgacc ctgcccgccg aggggagctg agcgtgtgtg acagtattag tgagtgggta 60
acggcggcag acaaaaagac tgcagtggac atgtcgggcg ggacggtcac agtccttgaa 120
aaggtccctg tatcaaaagg ccaactgaag caatacttct acgagaccaa gtgcaatccc 180
atgggttaca caaaagaagg ctgcaggggc atagacaaaa ggcattggaa ctcccagtgc 240
cgaactaccc agtcgtacgt gcgggccctt accatggata gcaaaaagag aattggctgg 300
cgattcataa ggatagacac ttcttgtgta tgtacattga ccattaaaag gggaaga 357

<210> 251
<211> 90
<212> DNA
<213> Homo sapiens

<400> 251
cacggtgaag gtactttcac ttctgatgtt tcttcttact tggaaggtca agctgctaag 60
gaattcattg cttggttggt taagggtaga 90

<210> 252
<211> 96
<212> DNA
<213> Homo sapiens

<400> 252
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 253
<211> 96
<212> DNA
<213> Homo sapiens

<400> 253
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 254
<211> 2004
<212> DNA
<213> Homo sapiens

<400> 254
atgaaggtct ccgtggctgc cctctcctgc ctcatgcttg ttactgccct tggatcccag 60
gcccacggtg aaggtacttt cacttctgat gtttcttctt acttggaagg tcaagctgct 120
aaggaattca ttgcttggtt ggttaagggt agacacggtg aaggtacttt cacttctgat 180
gtttcttctt acttggaagg tcaagctgct aaggaattca ttgcttggtt ggttaagggt 240
agagatgcac acaagagtga ggttgctcat cgatttaaag atttgggaga agaaaatttc 300
aaagccttgg tgttgattgc ctttgctcag tatcttcagc agtgtccatt tgaagatcat 360
gtaaaattag tgaatgaagt aactgaattt gcaaaaacat gtgttgctga tgagtcagct 420
gaaaattgtg acaaatcact tcataccctt tttggagaca aattatgcac agttgcaact 480
cttcgtgaaa cctatggtga aatggctgac tgctgtgcaa aacaagaacc tgagagaaat 540
gaatgcttct tgcaacacaa agatgacaac ccaaacctcc cccgattggt gagaccagag 600
gttgatgtga tgtgcactgc ttttcatgac aatgaagaga catttttgaa aaaatactta 660
tatgaaattg ccagaagaca tccttacttt tatgccccgg aactcctttt ctttgctaaa 720
aggtataaag ctgcttttac agaatgttgc caagctgctg ataaagctgc ctgcctgttg 780
ccaaagctcg atgaacttcg ggatgaaggg aaggcttcgt ctgccaaaca gagactcaag 840
tgtgccagtc tccaaaaatt tggagaaaga gctttcaaag catgggcagt agctcgcctg 900
agccagagat ttcccaaagc tgagtttgca gaagtttcca agttagtgac agatcttacc 960
aaagtccaca cggaatgctg ccatggagat ctgcttgaat gtgctgatga cagggcggac 1020
cttgccaagt atatctgtga aaatcaagat tcgatctcca gtaaactgaa ggaatgctgt 1080
gaaaaacctc tgttggaaaa atcccactgc attgccgaag tggaaaatga tgagatgcct 1140
gctgacttgc cttcattagc tgctgatttt gttgaaagta aggatgtttg caaaaactat 1200
gctgaggcaa aggatgtctt cctgggcatg tttttgtatg aatatgcaag aaggcatcct 1260

gattactctg tcgtgctgct gctgagactt gccaagacat atgaaaccac tctagagaag 1320
tgctgtgccg ctgcagatcc tcatgaatgc tatgccaaag tgttcgatga atttaaacct 1380
cttgtggaag agcctcagaa tttaatcaaa caaaattgtg agctttttga gcagcttgga 1440
gagtacaaat tccagaatgc gctattagtt cgttacacca agaaagtacc ccaagtgtca 1500
actccaactc ttgtagaggt ctcaagaaac ctaggaaaag tgggcagcaa atgttgtaaa 1560
catcctgaag caaaaagaat gccctgtgca gaagactatc tatccgtggt cctgaaccag 1620
ttatgtgtgt tgcatgagaa aacgccagta agtgacagag tcaccaaatg ctgcacagaa 1680
tccttggtga acaggcgacc atgcttttca gctctggaag tcgatgaaac atacgttccc 1740
aaagagttta atgctgaaac attcaccttc catgcagata tatgcacact ttctgagaag 1800
gagagacaaa tcaagaaaca aactgcactt gttgagctcg tgaaacacaa gcccaaggca 1860
acaaaagagc aactgaaagc tgttatggat gatttcgcag cttttgtaga gaagtgctgc 1920
aaggctgacg ataaggagac ctgctttgcc gaggagggta aaaaacttgt tgctgcaagt 1980
caagctgcct taggcttata ataa 2004

<210> 255
<211> 87
<212> DNA
<213> Homo sapiens

<400> 255
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctg 87

<210> 256
<211> 96
<212> DNA
<213> Homo sapiens

<400> 256
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 257
<211> 96
<212> DNA
<213> Homo sapiens

<400> 257
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 258
<211> 96
<212> DNA
<213> Homo sapiens

<400> 258
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 259
<211> 96
<212> DNA
<213> Homo sapiens

<400> 259
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 260
<211> 96

<212> DNA
<213> Homo sapiens

<400> 260
agccccaaga tggtgcaagg gtctggctgc tttgggggta agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 261
<211> 1716
<212> DNA
<213> Homo sapiens

<400> 261
atgtggtggc gcctgtggtg gctgctgctg ctgctgctgc tgctgtggcc catggtgtgg 60
gccagcccca agatggtgca agggtctggc tgctttggga ggaagatgga ccggatcagc 120
tcctccagtg gcctgggctg caaagtgctg tcacttcata cccttttgg agacaaatta 180
tgcacagttg caactcttcg tgaaacctat ggtgaaatgg ctgactgctg tgcaaaacaa 240
gaacctgaga gaaatgaatg cttcttgcaa cacaaagatg acaacccaaa cctcccccga 300
ttggtgagac cagaggttga tgtgatgtgc actgcttttc atgacaatga agagacattt 360
ttgaaaaaat acttatatga aattgccaga agacatcctt acttttatgc cccggaactc 420
cttttctttg ctaaaaggta taaagctgct tttacagaat gttgccaagc tgctgataaa 480
gctgcctgcc tgttgccaaa gctcgatgaa cttcgggatg aagggaaggc ttcgtctgcc 540
aaacagagac tcaagtgtgc cagtctccaa aaatttggag aaagagcttt caaagcatgg 600
gcagtagctc gcctgagcca gagatttccc aaagctgagt ttgcagaagt ttccaagtta 660
gtgacagatc ttaccaaagt ccacacggaa tgctgccatg gagatctgct tgaatgtgct 720
gatgacaggg cggaccttgc caagtatatc tgtgaaaatc aagattcgat ctccagtaaa 780
ctgaaggaat gctgtgaaaa acctctgttg gaaaaatccc actgcattgc cgaagtggaa 840
aatgatgaga tgcctgctga cttgccttca ttagctgctg attttgttga aagtaaggat 900
gtttgcaaaa actatgctga ggcaaaggat gtcttcctgg gcatgttttt gtatgaatat 960
gcaagaaggc atcctgatta ctctgtcgtg ctgctgctga gacttgccaa gacatatgaa 1020
accactctag agaagtgctg tgccgctgca gatcctcatg aatgctatgc caaagtgttc 1080
gatgaattta aacctcttgt ggaagagcct cagaatttaa tcaaacaaaa ttgtgagctt 1140
tttgagcagc ttggagagta caaattccag aatgcgctat tagttcgtta caccaagaaa 1200
gtaccccaag tgtcaactcc aactcttgta gaggtctcaa gaaacctagg aaaagtgggc 1260
agcaaatgtt gtaaacatcc tgaagcaaaa agaatgccct gtgcagaaga ctatctatcc 1320
gtggtcctga accagttatg tgtgttgcat gagaaaacgc cagtaagtga cagagtcacc 1380
aaatgctgca cagaatcctt ggtgaacagg cgaccatgct tttcagctct ggaagtcgat 1440
gaaacatacg ttcccaaaga gtttaatgct gaaacattca ccttccatgc agatatatgc 1500
acactttctg agaaggagag acaaatcaag aaacaaactg cacttgttga gctcgtgaaa 1560
cacaagccca aggcaacaaa agagcaactg aaagctgtta tggatgattt cgcagctttt 1620
gtagagaagt gctgcaaggc tgacgataag gagacctgct ttgccgagga gggtaaaaaa 1680
cttgttgctg caagtcaagc tgccttaggc ttataa 1716

<210> 262
<211> 96
<212> DNA
<213> Homo sapiens

<400> 262
agccccaaga tggtgcaagg gtctggctgc tttgggggca agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 263
<211> 96
<212> DNA
<213> Homo sapiens

<400> 263
agccccaaga tggtgcaagg gtctggctgc tttgggaggg gcatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 264
<211> 96
<212> DNA
<213> Homo sapiens

<400> 264
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 265
<211> 1929
<212> DNA
<213> Homo sapiens

<400> 265
atgaagtggg taagctttat ttcccttctt tttctcttta gctcggctta ttccaggagc 60
ctcgacaaaa gaagccccaa gatggtgcaa gggtctggct gctttgggag gaagatggac 120
cggatcagct cctccagtgg cctgggctgc aaagtgctga ggggtggtgg tgatgcacac 180
aagagtgagg ttgctcatcg atttaaagat ttgggagaag aaaatttcaa agccttggtg 240
ttgattgcct ttgctcagta tcttcagcag tgtccatttg aagatcatgt aaaattagtg 300
aatgaagtaa ctgaatttgc aaaaacatgt gttgctgatg agtcagctga aaattgtgac 360
aaatcacttc ataccctttt tggagacaaa ttatgcacag ttgcaactct tcgtgaaacc 420
tatggtgaaa tggctgactg ctgtgcaaaa caagaacctg agagaaatga atgcttcttg 480
caacacaaag atgacaaccc aaacctcccc cgattggtga gaccagaggt tgatgtgatg 540
tgcactgctt ttcatgacaa tgaagagaca tttttgaaaa aatacttata tgaaattgcc 600
agaagacatc cttactttta tgccccggaa ctccttttct ttgctaaaag gtataaagct 660
gcttttacag aatgttgcca agctgctgat aaagctgcct gcctgttgcc aaagctcgat 720
gaacttcggg atgaagggaa ggcttcgtct gccaaacaga gactcaagtg tgccagtctc 780
caaaaatttg gagaaagagc tttcaaagca tgggcagtag ctcgcctgag ccagagattt 840
cccaaagctg agtttgcaga agtttccaag ttagtgacag atcttaccaa agtccacacg 900
gaatgctgcc atggagatct gcttgaatgt gctgatgaca gggcggacct tgccaagtat 960
atctgtgaaa atcaagattc gatctccagt aaactgaagg aatgctgtga aaaacctctg 1020
ttggaaaaat cccactgcat tgccgaagtg gaaaatgatg agatgcctgc tgacttgcct 1080
tcattagctg ctgattttgt tgaaagtaag gatgtttgca aaaactatgc tgaggcaaag 1140
gatgtcttcc tgggcatgtt tttgtatgaa tatgcaagaa ggcatcctga ttactctgtc 1200
gtgctgctgc tgagacttgc caagacatat gaaaccactc tagagaagtg ctgtgccgct 1260
gcagatcctc atgaatgcta tgccaaagtg ttcgatgaat ttaaacctct tgtggaagag 1320
cctcagaatt taatcaaaca aaattgtgag ctttttgagc agcttggaga gtacaaattc 1380
cagaatgcgc tattagttcg ttacaccaag aaagtacccc aagtgtcaac tccaactctt 1440
gtagaggtct caagaaacct aggaaaagtg ggcagcaaat gttgtaaaca tcctgaagca 1500
aaaagaatgc cctgtgcaga agactatcta tccgtggtcc tgaaccagtt atgtgtgttg 1560
catgagaaaa cgccagtaag tgacagagtc accaaatgct gcacagaatc cttggtgaac 1620
aggcgaccat gcttttcagc tctggaagtc gatgaaacat acgttcccaa agagtttaat 1680
gctgaaacat tcaccttcca tgcagatata tgcacacttt ctgagaagga gagacaaatc 1740
aagaaacaaa ctgcacttgt tgagcttgtg aaacacaagc ccaaggcaac aaaagagcaa 1800
ctgaaagctg ttatggatga tttcgcagct tttgtagaga agtgctgcaa ggctgacgat 1860
aaggagacct gctttgccga ggagggtaaa aaacttgttg ctgcaagtca agctgcctta 1920
ggcttataa 1929

<210> 266
<211> 456
<212> DNA
<213> Homo sapiens

<400> 266
atgagctcct tctccaccac caccgtgagc ttcctccttt tactggcatt ccagctccta 60
ggtcagacca gagctaatcc catgtacaat gccgtgtcca acgcagacct gatggatttc 120
aagaatttgc tggaccattt ggaagaaaag atgcctttag aagatgaggt cgtgcccccca 180
caagtgctca gtgagccgaa tgaagaagcg gggctgctc tcagcccccct ccctgaggtg 240
cctcccctgga ccggggaagt cagcccagcc cagagagatg gaggtgccct cgggcggggc 300
ccctgggact cctctgatcg atctgccctc ctaaaaagca agctgagggc gctgctcact 360

gcccctcgga gcctgcggag atccagctgc ttcgggggca ggatggacag gattggagcc 420
cagagcggac tgggctgtaa cagcttccgg tactga 456

<210> 267
<211> 456
<212> DNA
<213> Homo sapiens

<400> 267
atgagctcct tctccaccac caccgtgagc ttcctccttt tactggcatt ccagctccta 60
ggtcagacca gagctaatcc catgtacaat gccgtgtcca acgcagacct gatggatttc 120
aagaatttgc tggaccattt ggaagaaaag atgcctttag aagatgaggt cgtgcccccca 180
caagtgctca gtgagccgaa tgaagaagcg ggggctgctc tcagcccccct ccctgaggtg 240
cctccctgga ccggggaagt cagcccagcc cagagagatg gaggtgccct cgggcggggc 300
ccctgggact cctctgatcg atctgccctc ctaaaaagca agctgagggc gctgctcact 360
gcccctcgga gcctgcggag atccagctgc ttcgggggca ggatggacag gattggagcc 420
cagagcggac tgggctgtaa cagcttccgg tactga 456

<210> 268
<211> 456
<212> DNA
<213> Homo sapiens

<400> 268
atgagctcct tctccaccac caccgtgagc ttcctccttt tactggcatt ccagctccta 60
ggtcagacca gagctaatcc catgtacaat gccgtgtcca acgcagacct gatggatttc 120
aagaatttgc tggaccattt ggaagaaaag atgcctttag aagatgaggt cgtgcccccca 180
caagtgctca gtgagccgaa tgaagaagcg ggggctgctc tcagcccccct ccctgaggtg 240
cctccctgga ccggggaagt cagcccagcc cagagagatg gaggtgccct cgggcggggc 300
ccctgggact cctctgatcg atctgccctc ctaaaaagca agctgagggc gctgctcact 360
gcccctcgga gcctgcggag atccagctgc ttcgggggca ggatggacag gattggagcc 420
cagagcggac tgggctgtaa cagcttccgg tactga 456

<210> 269
<211> 456
<212> DNA
<213> Homo sapiens

<400> 269
atgagctcct tctccaccac caccgtgagc ttcctccttt tactggcatt ccagctccta 60
ggtcagacca gagctaatcc catgtacaat gccgtgtcca acgcagacct gatggatttc 120
aagaatttgc tggaccattt ggaagaaaag atgcctttag aagatgaggt cgtgcccccca 180
caagtgctca gtgagccgaa tgaagaagcg ggggctgctc tcagcccccct ccctgaggtg 240
cctccctgga ccggggaagt cagcccagcc cagagagatg gaggtgccct cgggcggggc 300
ccctgggact cctctgatcg atctgccctc ctaaaaagca agctgagggc gctgctcact 360
gcccctcgga gcctgcggag atccagctgc ttcgggggca ggatggacag gattggagcc 420
cagagcggac tgggctgtaa cagcttccgg tactga 456

<210> 270
<211> 456
<212> DNA
<213> Homo sapiens

<400> 270
atgagctcct tctccaccac caccgtgagc ttcctccttt tactggcatt ccagctccta 60
ggtcagacca gagctaatcc catgtacaat gccgtgtcca acgcagacct gatggatttc 120
aagaatttgc tggaccattt ggaagaaaag atgcctttag aagatgaggt cgtgcccccca 180
caagtgctca gtgagccgaa tgaagaagcg ggggctgctc tcagcccccct ccctgaggtg 240
cctccctgga ccggggaagt cagcccagcc cagagagatg gaggtgccct cgggcggggc 300
ccctgggact cctctgatcg atctgccctc ctaaaaagca agctgagggc gctgctcact 360
gcccctcgga gcctgcggag atccagctgc ttcgggggca ggatggacag gattggagcc 420

cagagcggac tgggctgtaa cagcttccgg tactga 456

<210> 271
<211> 456
<212> DNA
<213> Homo sapiens

<400> 271
atgagctcct tctccaccac caccgtgagc ttcctccttt tactggcatt ccagctccta 60
ggtcagacca gagctaatcc catgtacaat gccgtgtcca acgcagacct gatggatttc 120
aagaatttgc tggaccattt ggaagaaaag atgcctttag aagatgaggt cgtgccccca 180
caagtgctca gtgagccgaa tgaagaagcg ggggctgctc tcagcccccct ccctgaggtg 240
cctccctgga ccggggaagt cagcccagcc cagagagatg gaggtgccct cgggcggggc 300
ccctgggact cctctgatcg atctgccctc ctaaaaagca agctgagggc gctgctcact 360
gcccctcgga gcctgcggag atccagctgc ttcgggggca ggatggacag gattggagcc 420
cagagcggac tgggctgtaa cagcttccgg tactga 456

<210> 272
<211> 381
<212> DNA
<213> Homo sapiens

<400> 272
atgcatctct cccagctgct ggcctgcgcc ctgctgctca cgctgctctc cctccggccc 60
tccgaagcca agcccggggc gccgccgaag gtcccgcgaa ccccgccggc agaggagctg 120
gccgagccgc aggctgcggg cggcggtcag aagaagggcg acaaggctcc cgggggcggg 180
ggcgccaatc tcaagggcga ccggtcgcga ctgctccggg acctgcgcgt ggacaccaag 240
tcgcgggcag cgtgggctcg ccttctgcaa gagcacccca acgcgcgcaa atacaaagga 300
gccaacaaga agggcttgtc caagggctgc ttcggcctca agctggaccg aatcggctcc 360
atgagcggcc tgggatgtta g 381

<210> 273
<211> 381
<212> DNA
<213> Homo sapiens

<400> 273
atgcatctct cccagctgct ggcctgcgcc ctgctgctca cgctgctctc cctccggccc 60
tccgaagcca agcccggggc gccgccgaag gtcccgcgaa ccccgccggc agaggagctg 120
gccgagccgc aggctgcggg cggcggtcag aagaagggcg acaaggctcc cgggggcggg 180
ggcgccaatc tcaagggcga ccggtcgcga ctgctccggg acctgcgcgt ggacaccaag 240
tcgcgggcag cgtgggctcg ccttctgcaa gagcacccca acgcgcgcaa atacaaagga 300
gccaacaaga agggcttgtc caagggctgc ttcggcctca agctggaccg aatcggctcc 360
atgagcggcc tgggatgtta g 381

<210> 274
<211> 114
<212> DNA
<213> Dendroaspis angusticeps

<400> 274
gaagttaagt acgatccatg tttcggtcac aagattgata gaattaacca cgtttctaac 60
ttgggttgtc catctttgag agatccaaga ccaaacgctc catctacttc tgct 114

<210> 275
<211> 114
<212> DNA
<213> Dendroaspis angusticeps

<400> 275
gaagttaagt acgatccatg tttcggtcac aagattgata gaattaacca cgtttctaac 60

ttgggttgtc catctttgag agatccaaga ccaaacgctc catctacttc tgct 114

<210> 276
<211> 1929
<212> DNA
<213> Homo sapiens

<400> 276
atgaagtggg taagctttat ttcccttctt tttctcttta gctcggctta ttccggtagc 60
ctcgacaaaa gaagccccaa gatggtgcaa gggtctggct gctttgggag gaagatggac 120
cggatcagct cctccagtgg cctgggctgc aaagtgctga ggggtggtgg tgatgcacac 180
aagagtgagg ttgctcatcg atttaaagat ttgggagaag aaaatttcaa agccttggtg 240
ttgattgcct ttgctcagta tcttcagcag tgtccatttg aagatcatgt aaaattagtg 300
aatgaagtaa ctgaatttgc aaaaacatgt gttgctgatg agtcagctga aaattgtgac 360
aaatcacttc ataccctttt tggagacaaa ttatgcacag ttgcaactct tcgtgaaacc 420
tatggtgaaa tggctgactg ctgtgcaaaa caagaacctg agagaaatga atgcttcttg 480
caacacaaag atgacaaccc aaacctcccc cgattggtga gaccagaggt tgatgtgatg 540
tgcactgctt ttcatgacaa tgaagagaca tttttgaaaa aatacttata tgaaattgcc 600
agaagacatc cttactttta tgccccggaa ctccttttct ttgctaaaag gtataaagct 660
gcttttacag aatgttgcca agctgctgat aaagctgcct gcctgttgcc aaagctcgat 720
gaacttcggg atgaagggaa ggcttcgtct gccaaacaga gactcaagtg tgccagtctc 780
caaaaatttg gagaaagagc tttcaaagca tggcagtag ctcgcctgag ccagagattt 840
cccaaagctg agtttgcaga agtttccaag ttagtgacag atcttaccaa agtccacacg 900
gaatgctgcc atggagatct gcttgaatgt gctgatgaca gggcggacct tgccaagtat 960
atctgtgaaa atcaagattc gatctccagt aaactgaagg aatgctgtga aaaacctctg 1020
ttggaaaaat cccactgcat tgccgaagtg gaaaatgatg agatgcctgc tgacttgcct 1080
tcattagctg ctgattttgt tgaaagtaag gatgtttgca aaaactatgc tgaggcaaag 1140
gatgtcttcc tgggcatgtt tttgtatgaa tatgcaagaa ggcatcctga ttactctgtc 1200
gtgctgctgc tgagacttgc caagacatat gaaaccactc tagagaagtg ctgtgccgct 1260
gcagatcctc atgaatgcta tgccaaagtg ttcgatgaat ttaaacctct tgtggaagag 1320
cctcagaatt taatcaaaca aaattgtgag ctttttgagc agcttggaga gtacaaattc 1380
cagaatgcgc tattagttcg ttacaccaag aaagtacccc aagtgtcaac tccaactctt 1440
gtagaggtct caagaaacct aggaaaagtg ggcagcaaat gttgtaaaca tcctgaagca 1500
aaaagaatgc cctgtgcaga agactatcta tccgtggtcc tgaaccagtt atgtgtgttg 1560
catgagaaaa cgccagtaag tgacagagtc accaaatgct gcacagaatc cttggtgaac 1620
aggcgaccat gcttttcagc tctggaagtc gatgaaacat acgttcccaa agagtttaat 1680
gctgaaacat tcaccttcca tgcagatata tgcacacttt ctgagaagga gagacaaatc 1740
aagaaacaaa ctgcacttgt tgagcttgtg aaacacaagc ccaaggcaac aaaagagcaa 1800
ctgaaagctg ttatggatga tttcgcagct tttgtagaga agtgctgcaa ggctgacgat 1860
aaggagacct gctttgccga ggagggtaaa aaacttgttg ctgcaagtca agctgcctta 1920
ggcttataa 1929

<210> 277
<211> 96
<212> DNA
<213> Homo sapiens

<400> 277
agccccaaga tggtgcaagg gtctggctgc tttgggaggg gcatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 278
<211> 96
<212> DNA
<213> Homo sapiens

<400> 278
agccccaaga tggtgcaagg gtctggctgc tttgggaggg gcatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 279

<211> 96
<212> DNA
<213> Homo sapiens

<400> 279
agccccaaga tggtgcaagg gtctggctgc tttgggaggg gcatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 280
<211> 96
<212> DNA
<213> Homo sapiens

<400> 280
agccccaaga tggtgcaagg gtctggctgc tttgggaggg gcatggaccg gatcagctcc 60
tccagtggcc tgggctgcaa agtgctgagg cggcat 96

<210> 281
<211> 912
<212> DNA
<213> Rattus norvegicus

<400> 281
atggcccatt accatgacga ctatggaaag aatgatgaag tggagtttgt ccgaactggc 60
tatgggaagg acatggtcaa agttctccat attcagaggg atggaaaata ccacagcatc 120
aaagaggtgg cgacttcggt gcagttgact ctgaggtcca aaaaggatta cctccatggt 180
gataattccg acatcatccc cacagacacc atcaagaaca cagtgcatgt cctggcgaag 240
ttcaaaggga tcaaaagcat cgagaccttc gctatgaaca tctgcgagca cttcctctct 300
tcctttagcc atgtcacccg agcccatgtc tacgtggaag aggtcccctg gaagcgtttt 360
gaaaagaatg gagtcaaaca cgtccatgcc ttcatccaca ccccgacggg aactcacttc 420
tgtgacgtgg agcaggtgag gaacggacct cccatcattc actctggaat caaagacctc 480
aaggtcttga aaacaaccca gtctggattt gaaggattca tcaaggacca gttcactact 540
ctccccgagg tgaaggaccg atgctttgcc actcaagtgt actgcaagtg gcgctaccag 600
aatcgggacg tggatttcga ggctacctgg ggcgctgtcc gggacattgt cctgaagaaa 660
tttgctgggc cctatgacag aggtgaatac tcaccttccg tgcagaagac cctctatgac 720
atacaagtgc tgaccctgag ccagcttcct gagatagaag acatggaaat cagccttcca 780
aacattcact actttaacat cgacatgtcc aaaatggggc tgatcaacaa ggaagaggtt 840
ttgctgcctc tggacaaccc ctacggcaaa ataaccggga cggtgaggag gaagctgcct 900
tccaggctgt ga 912

<210> 282
<211> 912
<212> DNA
<213> Rattus norvegicus

<400> 282
atggcccatt accatgacga ctatggaaag aatgatgaag tggagtttgt ccgaactggc 60
tatgggaagg acatggtcaa agttctccat attcagaggg atggaaaata ccacagcatc 120
aaagaggtgg cgacttcggt gcagttgact ctgaggtcca aaaaggatta cctccatggt 180
gataattccg acatcatccc cacagacacc atcaagaaca cagtgcatgt cctggcgaag 240
ttcaaaggga tcaaaagcat cgagaccttc gctatgaaca tctgcgagca cttcctctct 300
tcctttagcc atgtcacccg agcccatgtc tacgtggaag aggtcccctg gaagcgtttt 360
gaaaagaatg gagtcaaaca cgtccatgcc ttcatccaca ccccgacggg aactcacttc 420
tgtgacgtgg agcaggtgag gaacggacct cccatcattc actctggaat caaagacctc 480
aaggtcttga aaacaaccca gtctggattt gaaggattca tcaaggacca gttcactact 540
ctccccgagg tgaaggaccg atgctttgcc actcaagtgt actgcaagtg gcgctaccag 600
aatcgggacg tggatttcga ggctacctgg ggcgctgtcc gggacattgt cctgaagaaa 660
tttgctgggc cctatgacag aggtgaatac tcaccttccg tgcagaagac cctctatgac 720
atacaagtgc tgaccctgag ccagcttcct gagatagaag acatggaaat cagccttcca 780
aacattcact actttaacat cgacatgtcc aaaatggggc tgatcaacaa ggaagaggtt 840
ttgctgcctc tggacaaccc ctacggcaaa ataaccggga cggtgaggag gaagctgcct 900

tccaggctgt ga 912

<210> 283
<211> 1233
<212> DNA
<213> Mycoplasma arginini

<400> 283
atgtctgtat ttgacagtaa atttaaagga attcacgttt attcagaaat tggtgaatta 60
gaatcagttc tagttcacga accaggacgc gaaattgact atattacacc agctagacta 120
gatgaattat tattctcagc tatcttagaa agccacgatg ctagaaaaga acacaaacaa 180
ttcgtagcag aattaaaagc aaacgacatc aatgttgttg aattaattga tttagttgct 240
gaaacatatg atttagcatc acaagaagct aaagataaat taatcgaaga atttttagaa 300
gactcagaac cagttctatc agaagaacac aaagtagttg taagaaactt cttaaaagct 360
aaaaaaacat caagaaaatt agtagaaatc atgatggcag ggatcacaaa atacgattta 420
ggtatcgaag cagatcacga attaatcgtt gacccaatgc caaacctata cttcacacgt 480
gacccatttg catcagtagg taatggtgta acaatccact acatgcgtta caaagttaga 540
caacgtgaaa cattattctc aagatttgta ttctcaaatc accctaaact aattaacact 600
ccatggtact acgacccttc actaaaatta tcaatcgaag gtggagacgt atttatctac 660
aacaatgaca cattagtagt tggtgtttct gaaagaactg acttacaaac agttacttta 720
ttagctaaaa acattgttgc taataaagaa tgtgaattca aacgtattgt tgcaattaac 780
gttccaaaat ggacaaactt aatgcactta gacacatggc taacaatgtt agacaaggac 840
aaattcctat actcaccaat cgctaacgac gtatttaaat tctgggatta tgacttagta 900
aacggtggag cagaaccaca accagttgaa aacggattac ctctagaagg attattacaa 960
tcaatcatta acaaaaaacc agttttaatt cctatcgcag gtgaaggtgc ttcacaaatg 1020
gaaatcgaaa gagaaacaca cttcgatggt acaaactact tagcaattag accaggtgtt 1080
gtaattggtt actcacgtaa cgaaaaaaca aacgctgctc tagaagctgc aggcattaaa 1140
gttcttccat tccacggtaa ccaattatca ttaggtatgg gtaacgctcg ttgtatgtca 1200
atgcctttat cacgtaaaga tgttaagtgg tag 1233

<210> 284
<211> 1233
<212> DNA
<213> Mycoplasma arginini

<400> 284
atgtctgtat ttgacagtaa atttaaagga attcacgttt attcagaaat tggtgaatta 60
gaatcagttc tagttcacga accaggacgc gaaattgact atattacacc agctagacta 120
gatgaattat tattctcagc tatcttagaa agccacgatg ctagaaaaga acacaaacaa 180
ttcgtagcag aattaaaagc aaacgacatc aatgttgttg aattaattga tttagttgct 240
gaaacatatg atttagcatc acaagaagct aaagataaat taatcgaaga atttttagaa 300
gactcagaac cagttctatc agaagaacac aaagtagttg taagaaactt cttaaaagct 360
aaaaaaacat caagaaaatt agtagaaatc atgatggcag ggatcacaaa atacgattta 420
ggtatcgaag cagatcacga attaatcgtt gacccaatgc caaacctata cttcacacgt 480
gacccatttg catcagtagg taatggtgta acaatccact acatgcgtta caaagttaga 540
caacgtgaaa cattattctc aagatttgta ttctcaaatc accctaaact aattaacact 600
ccatggtact acgacccttc actaaaatta tcaatcgaag gtggagacgt atttatctac 660
aacaatgaca cattagtagt tggtgtttct gaaagaactg acttacaaac agttacttta 720
ttagctaaaa acattgttgc taataaagaa tgtgaattca aacgtattgt tgcaattaac 780
gttccaaaat ggacaaactt aatgcactta gacacatggc taacaatgtt agacaaggac 840
aaattcctat actcaccaat cgctaacgac gtatttaaat tctgggatta tgacttagta 900
aacggtggag cagaaccaca accagttgaa aacggattac ctctagaagg attattacaa 960
tcaatcatta acaaaaaacc agttttaatt cctatcgcag gtgaaggtgc ttcacaaatg 1020
gaaatcgaaa gagaaacaca cttcgatggt acaaactact tagcaattag accaggtgtt 1080
gtaattggtt actcacgtaa cgaaaaaaca aacgctgctc tagaagctgc aggcattaaa 1140
gttcttccat tccacggtaa ccaattatca ttaggtatgg gtaacgctcg ttgtatgtca 1200
atgcctttat cacgtaaaga tgttaagtgg tag 1233

<210> 285
<211> 1233
<212> DNA

<213> Mycoplasma arginini

<400> 285
```
atgtctgtat ttgacagtaa atttaaagga attcacgttt attcagaaat tggtgaatta     60
gaatcagttc tagttcacga accaggacgc gaaattgact atattacacc agctagacta    120
gatgaattat tattctcagc tatcttagaa agccacgatg ctagaaaaga acacaaacaa    180
ttcgtagcag aattaaaagc aaacgacatc aatgttgttg aattaattga tttagttgct    240
gaaacatatg atttagcatc acaagaagct aaagataaat taatcgaaga atttttagaa    300
gactcagaac cagttctatc agaagaacac aaagtagttg taagaaactt cttaaaagct    360
aaaaaaacat caagaaaatt agtagaaatc atgatggcag ggatcacaaa atacgattta    420
ggtatcgaag cagatcacga attaatcgtt gacccaatgc caaacctata cttcacacgt    480
gacccatttg catcagtagg taatggtgta acaatccact acatgcgtta caaagttaga    540
caacgtgaaa cattattctc aagatttgta ttctcaaatc accctaaact aattaacact    600
ccatggtact acgacccttc actaaaatta tcaatcgaag gtggagacgt atttatctac    660
aacaatgaca cattagtagt tggtgtttct gaaagaactg acttacaaac agttacttta    720
ttagctaaaa acattgttgc taataaagaa tgtgaattca aacgtattgt tgcaattaac    780
gttccaaaat ggacaaactt aatgcactta gacacatggc taacaatgtt agacaaggac    840
aaattcctat actcaccaat cgctaacgac gtatttaaat tctgggatta tgacttagta    900
aacggtggag cagaaccaca accagttgaa aacggattac ctctagaagg attattacaa    960
tcaatcatta acaaaaaacc agttttaatt cctatcgcag gtgaaggtgc ttcacaaatg   1020
gaaatcgaaa gagaaacaca cttcgatggt acaaactact tagcaattag accaggtgtt   1080
gtaattggtt actcacgtaa cgaaaaaaca aacgctgctc tagaagctgc aggcattaaa   1140
gttcttccat tccacggtaa ccaattatca ttaggtatgg gtaacgctcg ttgtatgtca   1200
atgcctttat cacgtaaaga tgttaagtgg tag                                1233
```

<210> 286
<211> 1233
<212> DNA
<213> Mycoplasma arginini

<400> 286
```
atgtctgtat ttgacagtaa atttaaagga attcacgttt attcagaaat tggtgaatta     60
gaatcagttc tagttcacga accaggacgc gaaattgact atattacacc agctagacta    120
gatgaattat tattctcagc tatcttagaa agccacgatg ctagaaaaga acacaaacaa    180
ttcgtagcag aattaaaagc aaacgacatc aatgttgttg aattaattga tttagttgct    240
gaaacatatg atttagcatc acaagaagct aaagataaat taatcgaaga atttttagaa    300
gactcagaac cagttctatc agaagaacac aaagtagttg taagaaactt cttaaaagct    360
aaaaaaacat caagaaaatt agtagaaatc atgatggcag ggatcacaaa atacgattta    420
ggtatcgaag cagatcacga attaatcgtt gacccaatgc caaacctata cttcacacgt    480
gacccatttg catcagtagg taatggtgta acaatccact acatgcgtta caaagttaga    540
caacgtgaaa cattattctc aagatttgta ttctcaaatc accctaaact aattaacact    600
ccatggtact acgacccttc actaaaatta tcaatcgaag gtggagacgt atttatctac    660
aacaatgaca cattagtagt tggtgtttct gaaagaactg acttacaaac agttacttta    720
ttagctaaaa acattgttgc taataaagaa tgtgaattca aacgtattgt tgcaattaac    780
gttccaaaat ggacaaactt aatgcactta gacacatggc taacaatgtt agacaaggac    840
aaattcctat actcaccaat cgctaacgac gtatttaaat tctgggatta tgacttagta    900
aacggtggag cagaaccaca accagttgaa aacggattac ctctagaagg attattacaa    960
tcaatcatta acaaaaaacc agttttaatt cctatcgcag gtgaaggtgc ttcacaaatg   1020
gaaatcgaaa gagaaacaca cttcgatggt acaaactact tagcaattag accaggtgtt   1080
gtaattggtt actcacgtaa cgaaaaaaca aacgctgctc tagaagctgc aggcattaaa   1140
gttcttccat tccacggtaa ccaattatca ttaggtatgg gtaacgctcg ttgtatgtca   1200
atgcctttat cacgtaaaga tgttaagtgg tag                                1233
```

<210> 287
<211> 390
<212> DNA
<213> Homo sapiens

<400> 287
```
atggctcggg gctcgctgcg ccggttgctg cggctcctcg tgctggggct ctggctggcg     60
ttgctgcgct ccgtggccgg ggagcaagcg ccaggcaccg ccccctgctc ccgcggcagc    120
```

```
tcctggagcg cggacctgga caagtgcatg gactgcgcgt cttgcagggc gcgaccgcac    180
agcgacttct gcctgggctg cgctgcagca cctcctgccc ccttccggct gctttggccc    240
atccttgggg gcgctctgag cctgaccttc gtgctggggc tgctttctgg ctttttggtc    300
tggagacgat gccgcaggag agagaagttc accaccccca tagaggagac cggcggagag    360
ggctgcccag ctgtggcgct gatccagtga                                     390
```

<210> 288
<211> 1494
<212> DNA
<213> Homo sapiens

<400> 288

```
gcccgcccct gcatccctaa aagcttcggc tacagctcgg tggtgtgtgt ctgcaatgcc     60
acatactgtg actcctttga ccccccgacc tttcctgccc ttggtacctt cagccgctat    120
gagagtacac gcagtgggcg acggatggag ctgagtatgg ggcccatcca ggctaatcac    180
acgggcacag gcctgctact gaccctgcag ccagaacaga agttccagaa agtgaaggga    240
tttggagggg ccatgacaga tgctgctgct ctcaacatcc ttgccctgtc acccccctgcc   300
caaaatttgc tacttaaatc gtacttctct gaagaaggaa tcggatataa catcatccgg    360
gtacccatgg ccagctgtga cttctccatc cgcacctaca cctatgcaga cacccctgat    420
gatttccagt tgcacaactt cagcctccca gaggaagata ccaagctcaa gatacccctg    480
attcaccgag ccctgcagtt ggcccagcgt cccgtttcac tccttgccag cccctggaca    540
tcacccactt ggctcaagac caatggagcg gtgaatggga aggggtcact caagggacag    600
cccggagaca tctaccacca gacctgggcc agatactttg tgaagttcct ggatgcctat    660
gctgagcaca agttacagtt ctgggcagtg acagctgaaa atgagccttc tgctgggctg    720
ttgagtggat acccccttcca gtgcctgggc ttcacccctg aacatcagcg agacttcatt   780
gcccgtgacc taggtcctac cctcgccaac agtactcacc acaatgtccg cctactcatg    840
ctggatgacc aacgcttgct gctgccccac tgggcaaagg tggtactgac agacccagaa    900
gcagctaaat atgttcatgg cattgctgta cattggtacc tggactttct ggctccagcc    960
aaagccaccc taggggagac acaccgcctg ttccccaaca ccatgctctt tgcctcagag   1020
gcctgtgtgg gctccaagtt ctgggagcag agtgtgcggc taggctcctg ggatcgaggg   1080
atgcagtaca gccacagcat catcacgaac ctcctgtacc atgtggtcgg ctggaccgac   1140
tggaaccttg ccctgaaccc cgaaggagga cccaattggg tgcgtaactt tgtcgacagt   1200
cccatcattg tagacatcac caaggacacg ttttacaaac agcccatgtt ctaccacctt   1260
ggccacttca gcaagttcat tcctgagggc tcccagagag tggggctggt tgccagtcag   1320
aagaacgacc tggacgcagt ggcactgatg catcccgatg gctctgctgt tgtggtcgtg   1380
ctaaaccgct cctctaagga tgtgcctctt accatcaagg atcctgctgt gggcttcctg   1440
gagacaatct cacctggcta ctccattcac acctacctgt ggcatcgcca gtga          1494
```

<210> 289
<211> 1494
<212> DNA
<213> Homo sapiens

<400> 289

```
gcccgcccct gcatccctaa aagcttcggc tacagctcgg tggtgtgtgt ctgcaatgcc     60
acatactgtg actcctttga ccccccgacc tttcctgccc ttggtacctt cagccgctat    120
gagagtacac gcagtgggcg acggatggag ctgagtatgg ggcccatcca ggctaatcac    180
acgggcacag gcctgctact gaccctgcag ccagaacaga agttccagaa agtgaaggga    240
tttggagggg ccatgacaga tgctgctgct ctcaacatcc ttgccctgtc acccccctgcc   300
caaaatttgc tacttaaatc gtacttctct gaagaaggaa tcggatataa catcatccgg    360
gtacccatgg ccagctgtga cttctccatc cgcacctaca cctatgcaga cacccctgat    420
gatttccagt tgcacaactt cagcctccca gaggaagata ccaagctcaa gatacccctg    480
attcaccgag ccctgcagtt ggcccagcgt cccgtttcac tccttgccag cccctggaca    540
tcacccactt ggctcaagac caatggagcg gtgaatggga aggggtcact caagggacag    600
cccggagaca tctaccacca gacctgggcc agatactttg tgaagttcct ggatgcctat    660
gctgagcaca agttacagtt ctgggcagtg acagctgaaa atgagccttc tgctgggctg    720
ttgagtggat acccccttcca gtgcctgggc ttcacccctg aacatcagcg agacttcatt   780
gcccgtgacc taggtcctac cctcgccaac agtactcacc acaatgtccg cctactcatg    840
ctggatgacc aacgcttgct gctgccccac tgggcaaagg tggtactgac agacccagaa    900
gcagctaaat atgttcatgg cattgctgta cattggtacc tggactttct ggctccagcc    960
aaagccaccc taggggagac acaccgcctg ttccccaaca ccatgctctt tgcctcagag   1020
```

gcctgtgtgg gctccaagtt ctgggagcag agtgtgcggc taggctcctg ggatcgaggg 1080
atgcagtaca gccacagcat catcacgaac ctcctgtacc atgtggtcgg ctggaccgac 1140
tggaaccttg ccctgaaccc cgaaggagga cccaattggg tgcgtaactt tgtcgacagt 1200
cccatcattg tagacatcac caaggacacg ttttacaaac agcccatgtt ctaccacctt 1260
ggccacttca gcaagttcat tcctgagggc tcccagagag tggggctggt tgccagtcag 1320
aagaacgacc tggacgcagt ggcactgatg catcccgatg gctctgctgt tgtggtcgtg 1380
ctaaaccgct cctctaagga tgtgcctctt accatcaagg atcctgctgt gggcttcctg 1440
gagacaatct cacctggcta ctccattcac acctacctgt ggcatcgcca gtga 1494

<210> 290
<211> 1494
<212> DNA
<213> Homo sapiens

<400> 290
gcccgcccct gcatccctaa aagcttcggc tacagctcgg tggtgtgtgt ctgcaatgcc 60
acatactgtg actcctttga ccccccgacc tttcctgccc ttggtacctt cagccgctat 120
gagagtacac gcagtgggcg acggatggag ctgagtatgg ggcccatcca ggctaatcac 180
acgggcacag gcctgctact gaccctgcag ccagaacaga agttccagaa agtgaaggga 240
tttggagggg ccatgacaga tgctgctgct ctcaacatcc ttgccctgtc acccccctgcc 300
caaaatttgc tacttaaatc gtacttctct gaagaaggaa tcggatataa catcatccgg 360
gtacccatgg ccagctgtga cttctccatc cgcacctaca cctatgcaga cacccctgat 420
gatttccagt tgcacaactt cagcctccca gaggaagata ccaagctcaa gatacccctg 480
attcaccgag ccctgcagtt ggcccagcgt cccgtttcac tccttgccag cccctggaca 540
tcacccactt ggctcaagac caatggagcg gtgaatggga aggggtcact caagggacag 600
cccggagaca tctaccacca gacctgggcc agatactttg tgaagttcct ggatgcctat 660
gctgagcaca agttacagtt ctgggcagtg acagctgaaa atgagccttc tgctgggctg 720
ttgagtggat acccccttcca gtgcctgggc ttcacccctg aacatcagcg agacttcatt 780
gcccgtgacc taggtcctac cctcgccaac agtactcacc acaatgtccg cctactcatg 840
ctggatgacc aacgcttgct gctgccccac tgggcaaagg tggtactgac agacccagaa 900
gcagctaaat atgttcatgg cattgctgta cattggtacc tggactttct ggctccagcc 960
aaagccaccc taggggagac acaccgcctg ttccccaaca ccatgctctt tgcctcagag 1020
gcctgtgtgg gctccaagtt ctgggagcag agtgtgcggc taggctcctg ggatcgaggg 1080
atgcagtaca gccacagcat catcacgaac ctcctgtacc atgtggtcgg ctggaccgac 1140
tggaaccttg ccctgaaccc cgaaggagga cccaattggg tgcgtaactt tgtcgacagt 1200
cccatcattg tagacatcac caaggacacg ttttacaaac agcccatgtt ctaccacctt 1260
ggccacttca gcaagttcat tcctgagggc tcccagagag tggggctggt tgccagtcag 1320
aagaacgacc tggacgcagt ggcactgatg catcccgatg gctctgctgt tgtggtcgtg 1380
ctaaaccgct cctctaagga tgtgcctctt accatcaagg atcctgctgt gggcttcctg 1440
gagacaatct cacctggcta ctccattcac acctacctgt ggcatcgcca gtga 1494

<210> 291
<211> 1494
<212> DNA
<213> Homo sapiens

<400> 291
gcccgcccct gcatccctaa aagcttcggc tacagctcgg tggtgtgtgt ctgcaatgcc 60
acatactgtg actcctttga ccccccgacc tttcctgccc ttggtacctt cagccgctat 120
gagagtacac gcagtgggcg acggatggag ctgagtatgg ggcccatcca ggctaatcac 180
acgggcacag gcctgctact gaccctgcag ccagaacaga agttccagaa agtgaaggga 240
tttggagggg ccatgacaga tgctgctgct ctcaacatcc ttgccctgtc acccccctgcc 300
caaaatttgc tacttaaatc gtacttctct gaagaaggaa tcggatataa catcatccgg 360
gtacccatgg ccagctgtga cttctccatc cgcacctaca cctatgcaga cacccctgat 420
gatttccagt tgcacaactt cagcctccca gaggaagata ccaagctcaa gatacccctg 480
attcaccgag ccctgcagtt ggcccagcgt cccgtttcac tccttgccag cccctggaca 540
tcacccactt ggctcaagac caatggagcg gtgaatggga aggggtcact caagggacag 600
cccggagaca tctaccacca gacctgggcc agatactttg tgaagttcct ggatgcctat 660
gctgagcaca agttacagtt ctgggcagtg acagctgaaa atgagccttc tgctgggctg 720
ttgagtggat acccccttcca gtgcctgggc ttcacccctg aacatcagcg agacttcatt 780
gcccgtgacc taggtcctac cctcgccaac agtactcacc acaatgtccg cctactcatg 840

ctggatgacc aacgcttgct gctgccccac tgggcaaagg tggtactgac agacccagaa 900
gcagctaaat atgttcatgg cattgctgta cattggtacc tggactttct ggctccagcc 960
aaagccaccc taggggagac acaccgcctg ttccccaaca ccatgctctt tgcctcagag 1020
gcctgtgtgg gctccaagtt ctgggagcag agtgtgcggc taggctcctg ggatcgaggg 1080
atgcagtaca gccacagcat catcacgaac ctcctgtacc atgtggtcgg ctggaccgac 1140
tggaaccttg ccctgaaccc cgaaggagga cccaattggg tgcgtaactt tgtcgacagt 1200
cccatcattg tagacatcac caaggacacg ttttacaaac agcccatgtt ctaccacctt 1260
ggccacttca gcaagttcat tcctgagggc tcccagagag tggggctggt tgccagtcag 1320
aagaacgacc tggacgcagt ggcactgatg catcccgatg gctctgctgt tgtggtcgtg 1380
ctaaaccgct cctctaagga tgtgcctctt accatcaagg atcctgctgt gggcttcctg 1440
gagacaatct cacctggcta ctccattcac acctacctgt ggcatcgcca gtga 1494

<210> 292
<211> 156
<212> DNA
<213> Homo sapiens

<400> 292
taccgccaga gcatgaacaa cttccagggc ctccggagct ttggctgccg cttcgggacg 60
tgcacggtgc agaagctggc acaccagatc taccagttca cagataagga caaggacaac 120
gtcgccccca ggagcaagat cagcccccag ggctac 156

<210> 293
<211> 156
<212> DNA
<213> Homo sapiens

<400> 293
taccgccaga gcatgaacaa cttccagggc ctccggagct ttggctgccg cttcgggacg 60
tgcacggtgc agaagctggc acaccagatc taccagttca cagataagga caaggacaac 120
gtcgccccca ggagcaagat cagcccccag ggctac 156

<210> 294
<211> 156
<212> DNA
<213> Homo sapiens

<400> 294
taccgccaga gcatgaacaa cttccagggc ctccggagct ttggctgccg cttcgggacg 60
tgcacggtgc agaagctggc acaccagatc taccagttca cagataagga caaggacaac 120
gtcgccccca ggagcaagat cagcccccag ggctac 156

<210> 295
<211> 156
<212> DNA
<213> Homo sapiens

<400> 295
taccgccaga gcatgaacaa cttccagggc ctccggagct ttggctgccg cttcgggacg 60
tgcacggtgc agaagctggc acaccagatc taccagttca cagataagga caaggacaac 120
gtcgccccca ggagcaagat cagcccccag ggctac 156

<210> 296
<211> 438
<212> DNA
<213> Homo sapiens

<400> 296
atgaactcac tggtttcttg gcagctactg cttttcctct gtgccaccca ctttggggag 60
ccattagaaa aggtggcctc tgtggggaat tctagaccca caggccagca gctagaatcc 120
ctgggcctcc tggcccccgg ggagcagagc ctgccgtgca ccgagaggaa gccagctgct 180

actgccaggc tgagccgtcg gggacctcg ctgtccccgc cccccgagag ctccgggagc 240
ccccagcagc cgggcctgtc cgcccccac agccgccaga tccccgcacc ccagggcgcg 300
gtgctggtgc agcgggagaa ggacctgccg aactacaact ggaactcctt cggcctgcgc 360
ttcggcaagc gggaggcggc accagggaac cacggcagaa gcgctgggcg gggctggggc 420
gcaggtgcgg ggcagtga 438

<210> 297
<211> 438
<212> DNA
<213> Homo sapiens

<400> 297
atgaactcac tggtttcttg gcagctactg cttttcctct gtgccaccca ctttggggag 60
ccattagaaa aggtggcctc tgtggggaat tctagaccca caggccagca gctagaatcc 120
ctgggcctcc tggcccccgg ggagcagagc ctgccgtgca ccgagaggaa gccagctgct 180
actgccaggc tgagccgtcg gggacctcg ctgtccccgc cccccgagag ctccgggagc 240
ccccagcagc cgggcctgtc cgcccccac agccgccaga tccccgcacc ccagggcgcg 300
gtgctggtgc agcgggagaa ggacctgccg aactacaact ggaactcctt cggcctgcgc 360
ttcggcaagc gggaggcggc accagggaac cacggcagaa gcgctgggcg gggctggggc 420
gcaggtgcgg ggcagtga 438

<210> 298
<211> 1041
<212> DNA
<213> Homo sapiens

<400> 298
atggctcggc ctgggcagcg ttggctcggc aagtggcttg tggcgatggt cgtgtgggcg 60
ctgtgccggc tcgccacacc gctggccaag aacctggagc ccgtatcctg gagctccctc 120
aaccccaagt tcctgagtgg gaagggcttg gtgatctatc cgaaaattgg agacaagctg 180
gacatcatct gcccccgagc agaagcaggg cggccctatg agtactacaa gctgtacctg 240
gtgcggcctg agcaggcagc tgcctgtagc acagttctcg accccaacgt gttggtcacc 300
tgcaataggc cagagcagga aatacgcttt accatcaagt tccaggagtt cagccccaac 360
tacatgggcc tggagttcaa gaagcaccat gattactaca ttacctcaac atccaatgga 420
agcctggagg ggctggaaaa ccgggagggc ggtgtgtgcc gcacacgcac catgaagatc 480
atcatgaagg ttgggcaaga tcccaatgct gtgacgcctg agcagctgac taccagcagg 540
cccagcaagg aggcagacaa cactgtcaag atggccacac aggcccctgg tagtcggggc 600
tccctgggtg actctgatgg caagcatgag actgtgaacc aggaagagaa gagtggccca 660
ggtgcaagtg gggcagcag cggggaccct gatggcttct tcaactccaa ggtggcattg 720
ttcgcggctg tcggtgccgg ttgcgtcatc ttcctgctca tcatcatctt cctgacggtc 780
ctactactga agctacgcaa gcggcaccgc aagcacacac agcagcgggc ggctgccctc 840
tcgctcagta ccctggccag tcccaagggg ggcagtggca cagcgggcac cgagcccagc 900
gacatcatca ttcccttacg gactacagag aacaactact gcccccacta tgagaaggtg 960
agtggggact acgggcaccc tgtctacatc gtccaagaga tgccgcccca gagcccggcg 1020
aacatctact acaaggtctg a 1041

<210> 299
<211> 1041
<212> DNA
<213> Homo sapiens

<400> 299
atggctcggc ctgggcagcg ttggctcggc aagtggcttg tggcgatggt cgtgtgggcg 60
ctgtgccggc tcgccacacc gctggccaag aacctggagc ccgtatcctg gagctccctc 120
aaccccaagt tcctgagtgg gaagggcttg gtgatctatc cgaaaattgg agacaagctg 180
gacatcatct gcccccgagc agaagcaggg cggccctatg agtactacaa gctgtacctg 240
gtgcggcctg agcaggcagc tgcctgtagc acagttctcg accccaacgt gttggtcacc 300
tgcaataggc cagagcagga aatacgcttt accatcaagt tccaggagtt cagccccaac 360
tacatgggcc tggagttcaa gaagcaccat gattactaca ttacctcaac atccaatgga 420
agcctggagg ggctggaaaa ccgggagggc ggtgtgtgcc gcacacgcac catgaagatc 480
atcatgaagg ttgggcaaga tcccaatgct gtgacgcctg agcagctgac taccagcagg 540

cccagcaagg aggcagacaa cactgtcaag atggccacac aggcccctgg tagtcggggc 600
tccctgggtg actctgatgg caagcatgag actgtgaacc aggaagagaa gagtggccca 660
ggtgcaagtg gggcagcag cggggaccct gatggcttct tcaactccaa ggtggcattg 720
ttcgcggctg tcggtgccgg ttgcgtcatc ttcctgctca tcatcatctt cctgacggtc 780
ctactactga agctacgcaa gcggcaccgc aagcacacac agcagcgggc ggctgccctc 840
tcgctcagta ccctggccag tcccaagggg ggcagtggca cagcgggcac cgagcccagc 900
gacatcatca ttcccttacg gactacagag aacaactact gcccccacta tgagaaggtg 960
agtggggact acgggcaccc tgtctacatc gtccaagaga tgccgcccca gagcccggcg 1020
aacatctact acaaggtctg a 1041

<210> 300
<211> 390
<212> DNA
<213> Homo sapiens

<400> 300
atggctcggg gctcgctgcg ccggttgctg cggctcctcg tgctggggct ctggctggcg 60
ttgctgcgct ccgtggccgg ggagcaagcg ccaggcaccg ccccctgctc ccgcggcagc 120
tcctggagcg cggacctgga caagtgcatg gactgcgcgt cttgcagggc gcgaccgcac 180
agcgacttct gcctgggctg cgctgcagca cctcctgccc ccttccggct gctttggccc 240
atccttgggg gcgctctgag cctgaccttc gtgctggggc tgctttctgg ctttttggtc 300
tggagacgat gccgcaggag agagaagttc accaccccca tagaggagac cggcggagag 360
ggctgcccag ctgtggcgct gatccagtga 390

<210> 301
<211> 741
<212> DNA
<213> Homo sapiens

<400> 301
atgctgcgtc ggcgggggcag ccctggcatg ggtgtgcatg tgggtgcagc cctgggagca 60
ctgtggttct gcctcacagg agccctggag gtccaggtcc ctgaagaccc agtggtggca 120
ctggtgggca ccgatgccac cctgtgctgc tccttctccc ctgagcctgg cttcagcctg 180
gcacagctca acctcatctg gcagctgaca gacaccaaac agctggtgca cagctttgct 240
gagggccagg accagggcag cgcctatgcc aaccgcacgg ccctcttcct ggacctgctg 300
gcacagggca acgcatccct gaggctgcag cgcgtgcgtg tggcggacga gggcagcttc 360
acctgcttcg tgagcatccg ggatttcggc agcgctgccg tcagcctgca ggtggccgct 420
ccctactcga agcccagcat gaccctggag cccaacaagg acctgcggcc aggggacacg 480
gtgaccatca cgtgctccag ctaccggggc taccctgagg ctgaggtgtt ctggcaggat 540
gggcagggtg tgcccctgac tggcaacgtg accacgtcgc agatggccaa cgagcagggc 600
ttgtttgatg tgcacagcgt cctgcgggtg gtgctgggtg cgaatggcac ctacagctgc 660
ctggtgcgca accccgtgct gcagcaggat gcgcacggct ctgtcaccat cacagggcag 720
cctatgacat tccccccaga g 741

<210> 302
<211> 1041
<212> DNA
<213> Homo sapiens

<400> 302
atggctcggc ctgggcagcg ttggctcggc aagtggcttg tggcgatggt cgtgtgggcg 60
ctgtgccggc tcgccacacc gctggccaag aacctggagc ccgtatcctg gagctccctc 120
aaccccaagt tcctgagtgg gaagggcttg gtgatctatc cgaaaattgg agacaagctg 180
gacatcatct gcccccgagc agaagcaggg cggccctatg agtactacaa gctgtacctg 240
gtgcggcctg agcaggcagc tgcctgtagc acagttctcg accccaacgt gttggtcacc 300
tgcaataggc cagagcagga aatacgcttt accatcaagt tccaggagtt cagccccaac 360
tacatgggcc tggagttcaa gaagcaccat gattactaca ttacctcaac atccaatgga 420
agcctggagg ggctggaaaa ccgggagggc ggtgtgtgcc gcacacgcac catgaagatc 480
atcatgaagg ttgggcaaga tcccaatgct gtgacgcctg agcagctgac taccagcagg 540
cccagcaagg aggcagacaa cactgtcaag atggccacac aggcccctgg tagtcggggc 600
tccctgggtg actctgatgg caagcatgag actgtgaacc aggaagagaa gagtggccca 660

```
ggtgcaagtg ggggcagcag cggggaccct gatggcttct tcaactccaa ggtggcattg    720
ttcgcggctg tcggtgccgg ttgcgtcatc ttcctgctca tcatcatctt cctgacggtc    780
ctactactga agctacgcaa gcggcaccgc aagcacacac agcagcgggc ggctgccctc    840
tcgctcagta ccctggccag tcccaagggg ggcagtggca cagcgggcac cgagcccagc    900
gacatcatca ttcccttacg gactacagag aacaactact gcccccacta tgagaaggtg    960
agtggggact acgggcaccc tgtctacatc gtccaagaga tgccgcccca gagcccggcg   1020
aacatctact acaaggtctg a                                              1041
```

<210> 303
<211> 1041
<212> DNA
<213> Homo sapiens

<400> 303

```
atggctcggc ctgggcagcg ttggctcggc aagtggcttg tggcgatggt cgtgtgggcg     60
ctgtgccggc tcgccacacc gctggccaag aacctggagc ccgtatcctg gagctccctc    120
aaccccaagt tcctgagtgg gaagggcttg gtgatctatc cgaaaattgg agacaagctg    180
gacatcatct gcccccgagc agaagcaggg cggccctatg agtactacaa gctgtacctg    240
gtgcggcctg agcaggcagc tgcctgtagc acagttctcg accccaacgt gttggtcacc    300
tgcaataggc cagagcagga aatacgcttt accatcaagt tccaggagtt cagccccaac    360
tacatgggcc tggagttcaa gaagcaccat gattactaca ttacctcaac atccaatgga    420
agcctggagg ggctggaaaa ccgggagggc ggtgtgtgcc gcacacgcac catgaagatc    480
atcatgaagg ttgggcaaga tcccaatgct gtgacgcctg agcagctgac taccagcagg    540
cccagcaagg aggcagacaa cactgtcaag atggccacac aggcccctgg tagtcggggc    600
tccctgggtg actctgatgg caagcatgag actgtgaacc aggaagagaa gagtggccca    660
ggtgcaagtg ggggcagcag cggggaccct gatggcttct tcaactccaa ggtggcattg    720
ttcgcggctg tcggtgccgg ttgcgtcatc ttcctgctca tcatcatctt cctgacggtc    780
ctactactga agctacgcaa gcggcaccgc aagcacacac agcagcgggc ggctgccctc    840
tcgctcagta ccctggccag tcccaagggg ggcagtggca cagcgggcac cgagcccagc    900
gacatcatca ttcccttacg gactacagag aacaactact gcccccacta tgagaaggtg    960
agtggggact acgggcaccc tgtctacatc gtccaagaga tgccgcccca gagcccggcg   1020
aacatctact acaaggtctg a                                              1041
```

<210> 304
<211> 960
<212> DNA
<213> Pan troglodytes

<220>
<221> misc_difference
<222> (88) to (90)
<223> Natural stop codon replaced by Arg

<400> 304

```
atgcctgtgt tttcattgca gaatgatgag gtggagtttg tccgaactgg ctatgggaag     60
gatatagtaa aagttctcca tattcagcga gatggaaaat atcacagcat taaagaggtg    120
gcaacttcag tgcaacttac tctaagttcc aaaaaagatt acctgcatgg agataattca    180
gacatcatcc ctacagacac catcaagaac acagttcatg tcttggcaaa gtttaaagaa    240
aatgaaccag caaacataga tggggctatg gaaaaagcat tttgtttctt tttacaaatc    300
aaaagcatag aagcctttgg tgtgaatatt tgtgagcatt ttctttcttc ttttaaccat    360
gtaatccgag ctcaagtcta tgtggaagaa atcccttgga agcatcttga aaagaatgga    420
gttaagcatg tccatgcatt tattcacact cccactggaa cacacttcgg tgaagttgaa    480
cagctgagaa gtggacccca agtcattcat tctggaatca aagacctcaa gctcttgaaa    540
acaacacagt ctggatttga aggtttcatc aaggaccagt tcactaccct ccctgaggtt    600
tttaaatgca tgatgagaac gttacctcag tcttctttcc ctttatttca agtgctctcc    660
atgggcagca gcctgatgga caccattcgg gaccttgtca tggagaaatc tgctgggccc    720
tatgacaaag atgaatactc gccctctgtg cagaagaccc tctgtgatat ccaggtgctc    780
tccctgagcc gagttcctgc gatagaagat atggaaatca gcctgccaaa cattcactac    840
ttcaacatag acatgtccaa aatgggtctg atcaacaagg aagaggtctt gctgccatta    900
gacaatccat atggaaaaat tactggtaca gtcaagagga agttgtcttc aagactgtga    960
```

<210> 305
<211> 960
<212> DNA
<213> Pan troglodytes

<220>
<221> misc_difference
<222> (88) to (90)
<223> Natural stop codon replaced by Arg

<400> 305
atgcctgtgt tttcattgca gaatgatgag gtggagtttg tccgaactgg ctatgggaag 60
gatatagtaa aagttctcca tattcagcga gatggaaaat atcacagcat taaagaggtg 120
gcaacttcag tgcaacttac tctaagttcc aaaaaagatt acctgcatgg agataattca 180
gacatcatcc ctacagacac catcaagaac acagttcatg tcttggcaaa gtttaaagaa 240
aatgaaccag caaacataga tggggctatg gaaaaagcat tttgtttctt tttacaaatc 300
aaaagcatag aagcctttgg tgtgaatatt tgtgagcatt ttctttcttc ttttaaccat 360
gtaatccgag ctcaagtcta tgtggaagaa atcccttgga agcatcttga aaagaatgga 420
gttaagcatg tccatgcatt tattcacact cccactggaa cacacttcgg tgaagttgaa 480
cagctgagaa gtggacccca agtcattcat tctggaatca aagacctcaa gctcttgaaa 540
acaacacagt ctggatttga aggtttcatc aaggaccagt tcactaccct ccctgaggtt 600
tttaaatgca tgatgagaac gttacctcag tcttctttcc ctttatttca agtgctctcc 660
atgggcagca gcctgatgga caccattcgg gaccttgtca tggagaaatc tgctgggccc 720
tatgacaaag atgaatactc gccctctgtg cagaagaccc tctgtgatat ccaggtgctc 780
tccctgagcc gagttcctgc gatagaagat atggaaatca gcctgccaaa cattcactac 840
ttcaacatag acatgtccaa aatgggtctg atcaacaagg aagaggtctt gctgccatta 900
gacaatccat atggaaaaat tactggtaca gtcaagagga agttgtcttc aagactgtga 960

<210> 306
<211> 1186
<212> DNA
<213> Homo sapiens

<220>
<221> misc_difference
<222> (310) to (312)
<223> Natural stop codon replaced by Arg

<220>
<221> misc_difference
<222> (829) to (831)
<223> Natural stop codon replaced by Arg

<220>
<221> misc_feature
<222> (1186)
<223> n equals a,t,g, or c

<400> 306
atggagaaat tcatttggta cctggtgcat ttgtacactg aaatgaccaa gtcttctccc 60
tcctgccgcc tcgtggctag ttgtcagacc gtggcaaaag aactgggga gaacagcctc 120
ggttatggtc caggccatta tctgctcttt gggtgcaggg atgcttttgg gtgtcccatg 180
ccaggcttgt tccacctgct ccaggatcag atgattggtt cccttcatac agactcattg 240
ccaaatgatg aggtggagtt tgtccgaact ggctatggga aggaaatggt aaaagttctc 300
catattcagc gagatggaaa atatcacagc attaaagagg tggcaacttc agtgcaactt 360
actctaagtt ccaaaaaaga ttacctgcat ggagataatt cagacatcat ccctacagac 420
accatcaaga acacagttca tgtcttggca aagtttaaag aaaatgaccc agcaaacata 480
gatggggcta tggaaaaagc atttgtttc tttttacaaa tcaaaagcat agaagccttt 540
ggtgtgaata tttgtgagca ttttctttct tcttttaacc atgtaatccg agctcaagtc 600
tacatggaag aaatcccttg gaagcatctt ggaaagaatg gagttaagca tgtccatgca 660
tttattcaca ctcccactgg aacacacttc tgtgaagttg aacagctgag aagtggaccc 720

caagtcattc attctggaat caaagacctc aaggtcttga aaacaacaca gtctggattt 780
gaaggtttca tcaaggacca gttcactacc ctccctgagg tgaaggaccg atgctttgcc 840
acccaagtgt actgcaagtg gcgctaccac cagtgcaggg atgtggactt caaggctacc 900
tgggacacca ttcgggacct tgtcatggag aaatctgctg ggccctatga caaaggtgaa 960
tacttgacct ctgtgcagaa gaccctctgt gatatccagg tgctctccct gagccgagtt 1020
cctgcgatag aagatatgga aatcagcctg ccaaacattc actacttcaa catagacatg 1080
tccaaaatgg gtctgatcaa caaggaagag gtcttgctgc cattagacaa tccatatgga 1140
aaaattactg gtacagtcaa gaggaagttg tcttcaagac tgtgan 1186

<210> 307
<211> 1186
<212> DNA
<213> Homo sapiens

<220>
<221> misc_difference
<222> (310) to (312)
<223> Natural stop codon replaced by Arg

<220>
<221> misc_difference
<222> (829) to (831)
<223> Natural stop codon replaced by Arg

<220>
<221> misc_feature
<222> (1186)
<223> n equals a,t,g, or c

<400> 307
atggagaaat tcatttggta cctggtgcat ttgtacactg aaatgaccaa gtcttctccc 60
tcctgccgcc tcgtggctag ttgtcagacc gtggcaaaag aactgggggga gaacagcctc 120
ggttatggtc caggccatta tctgctcttt gggtgcaggg atgcttttgg gtgtcccatg 180
ccaggcttgt tccacctgct ccaggatcag atgattggtt cccttcatac agactcattg 240
ccaaatgatg aggtggagtt tgtccgaact ggctatggga aggaaatggt aaaagttctc 300
catattcagc gagatggaaa atatcacagc attaaagagg tggcaacttc agtgcaactt 360
actctaagtt ccaaaaaaga ttacctgcat ggagataatt cagacatcat ccctacagac 420
accatcaaga acacagttca tgtcttggca aagtttaaag aaaatgaccc agcaaacata 480
gatggggcta tggaaaaagc attttgtttc tttttacaaa tcaaaagcat agaagccttt 540
ggtgtgaata tttgtgagca ttttctttct tcttttaacc atgtaatccg agctcaagtc 600
tacatggaag aaatcccttg gaagcatctt ggaaagaatg gagttaagca tgtccatgca 660
tttattcaca ctcccactgg aacacacttc tgtgaagttg aacagctgag aagtggaccc 720
caagtcattc attctggaat caaagacctc aaggtcttga aaacaacaca gtctggattt 780
gaaggtttca tcaaggacca gttcactacc ctccctgagg tgaaggaccg atgctttgcc 840
acccaagtgt actgcaagtg gcgctaccac cagtgcaggg atgtggactt caaggctacc 900
tgggacacca ttcgggacct tgtcatggag aaatctgctg ggccctatga caaaggtgaa 960
tacttgacct ctgtgcagaa gaccctctgt gatatccagg tgctctccct gagccgagtt 1020
cctgcgatag aagatatgga aatcagcctg ccaaacattc actacttcaa catagacatg 1080
tccaaaatgg gtctgatcaa caaggaagag gtcttgctgc cattagacaa tccatatgga 1140
aaaattactg gtacagtcaa gaggaagttg tcttcaagac tgtgan 1186

<210> 308
<211> 927
<212> DNA
<213> Papio hamadryas

<220>
<221> misc_feature
<222> (927)
<223> n equals a,t,g, or c

<400> 308
atggccgact accataacaa ctataaaaag aatgatgaat tggagtttgt ccgaactggc 60
tatgggaagg atatggtaaa agttctccat attcagcgag atggaaaata tcacagcatt 120
aaagaggtgg caacttcagt gcaacttact ctgagttcca aaaaagatta cctgcatgga 180
gataattcag atatcatccc tacagacacc atcaagaaca cagttcatgt cttggcaaag 240
tttaagggaa tcaaaagcat agaagccttt ggtgtgaata tttgtgagta ttttctttct 300
tcttttaacc atgtaatccg agctcaagtc tacgtggaag aaatcccttg gaagcgtctt 360
gaaaagaatg gagttaagca tgtccatgca tttattcaca ctcccactgg aacacacttc 420
tgtgaagttg aacaactgag aagtggaccc cccgtcatta cttctggaat caaagacctc 480
aaggtcttga aaacaacaca gtctggattt gaaggtttca tcaaggacca gttcaccacc 540
ctccctgagg tgaaggaccg atgctttgcc acccaagtgt actgcaagtg gcgctaccac 600
cagtgcaggg atgtggactt cgaggctacc tggggcacca ttcgggacct tgtcctggag 660
aaatttgctg ggccctatga caaaggcgag tactcaccct ctgtgcagaa gaccctctat 720
gatatccagg tgctctccct gagccgagtt cctgagatag aagatatgga aatcagcctg 780
ccaaacattc actacttcaa tatagacatg tccaaaatgg gtctgatcaa caaggaagag 840
gtcttgctgc cattagacaa tccatatgga aaaattactg gtacagtcaa gaggaagttg 900
tcttcaagac tgtgacattg tggccan 927

<210> 309
<211> 927
<212> DNA
<213> Papio hamadryas

<220>
<221> misc_feature
<222> (927)
<223> n equals a,t,g, or c

<400> 309
atggccgact accataacaa ctataaaaag aatgatgaat tggagtttgt ccgaactggc 60
tatgggaagg atatggtaaa agttctccat attcagcgag atggaaaata tcacagcatt 120
aaagaggtgg caacttcagt gcaacttact ctgagttcca aaaaagatta cctgcatgga 180
gataattcag atatcatccc tacagacacc atcaagaaca cagttcatgt cttggcaaag 240
tttaagggaa tcaaaagcat agaagccttt ggtgtgaata tttgtgagta ttttctttct 300
tcttttaacc atgtaatccg agctcaagtc tacgtggaag aaatcccttg gaagcgtctt 360
gaaaagaatg gagttaagca tgtccatgca tttattcaca ctcccactgg aacacacttc 420
tgtgaagttg aacaactgag aagtggaccc cccgtcatta cttctggaat caaagacctc 480
aaggtcttga aaacaacaca gtctggattt gaaggtttca tcaaggacca gttcaccacc 540
ctccctgagg tgaaggaccg atgctttgcc acccaagtgt actgcaagtg gcgctaccac 600
cagtgcaggg atgtggactt cgaggctacc tggggcacca ttcgggacct tgtcctggag 660
aaatttgctg ggccctatga caaaggcgag tactcaccct ctgtgcagaa gaccctctat 720
gatatccagg tgctctccct gagccgagtt cctgagatag aagatatgga aatcagcctg 780
ccaaacattc actacttcaa tatagacatg tccaaaatgg gtctgatcaa caaggaagag 840
gtcttgctgc cattagacaa tccatatgga aaaattactg gtacagtcaa gaggaagttg 900
tcttcaagac tgtgacattg tggccan 927

<210> 310
<211> 1186
<212> DNA
<213> Homo sapiens

<220>
<221> misc_difference
<222> (310) to (312)
<223> Natural stop codon replaced by Arg

<220>
<221> misc_difference
<222> (829) to (831)
<223> Natural stop codon replaced by Arg

<220>
<221> misc_feature
<222> (1186)
<223> n equals a,t,g, or c

<400> 310
atggagaaat tcatttggta cctggtgcat ttgtacactg aaatgaccaa gtcttctccc 60
tcctgccgcc tcgtggctag ttgtcagacc gtggcaaaag aactggggga gaacagcctc 120
ggttatggtc caggccatta tctgctcttt gggtgcaggg atgcttttgg gtgtcccatg 180
ccaggcttgt tccacctgct ccaggatcag atgattggtt cccttcatac agactcattg 240
ccaaatgatg aggtggagtt tgtccgaact ggctatggga aggaaatggt aaaagttctc 300
catattcagc gagatggaaa atatcacagc attaaagagg tggcaacttc agtgcaactt 360
actctaagtt ccaaaaaaga ttacctgcat ggagataatt cagacatcat ccctacagac 420
accatcaaga acacagttca tgtcttggca aagtttaaag aaaatgaccc agcaaacata 480
gatggggcta tggaaaaagc attttgtttc tttttacaaa tcaaaagcat agaagccttt 540
ggtgtgaata tttgtgagca ttttctttct tcttttaacc atgtaatccg agctcaagtc 600
tacatggaag aaatcccttg gaagcatctt ggaaagaatg gagttaagca tgtccatgca 660
tttattcaca ctcccactgg aacacacttc tgtgaagttg aacagctgag aagtggaccc 720
caagtcattc attctggaat caaagacctc aaggtcttga aaacaacaca gtctggattt 780
gaaggtttca tcaaggacca gttcactacc ctccctgagg tgaaggaccg atgctttgcc 840
acccaagtgt actgcaagtg gcgctaccac cagtgcaggg atgtggactt caaggctacc 900
tgggacacca ttcgggacct tgtcatggag aaatctgctg ggccctatga caaaggtgaa 960
tacttgacct ctgtgcagaa gaccctctgt gatatccagg tgctctccct gagccgagtt 1020
cctgcgatag aagatatgga aatcagcctg ccaaacattc actacttcaa catagacatg 1080
tccaaaatgg gtctgatcaa caaggaagag gtcttgctgc cattagacaa tccatatgga 1140
aaaattactg gtacagtcaa gaggaagttg tcttcaagac tgtgan 1186

<210> 311
<211> 960
<212> DNA
<213> Pan troglodytes

<220>
<221> misc_difference
<222> (88) to (90)
<223> Natural stop codon replaced by Arg

<400> 311
atgcctgtgt tttcattgca gaatgatgag gtggagtttg tccgaactgg ctatgggaag 60
gatatagtaa aagttctcca tattcagcga gatggaaaat atcacagcat taaagaggtg 120
gcaacttcag tgcaacttac tctaagttcc aaaaaagatt acctgcatgg agataattca 180
gacatcatcc ctacagacac catcaagaac acagttcatg tcttggcaaa gtttaaagaa 240
aatgaaccag caaacataga tggggctatg gaaaaagcat tttgtttctt tttacaaatc 300
aaaagcatag aagcctttgg tgtgaatatt tgtgagcatt ttctttcttc ttttaaccat 360
gtaatccgag ctcaagtcta tgtggaagaa atcccttgga agcatcttga aaagaatgga 420
gttaagcatg tccatgcatt tattcacact cccactggaa cacacttcgg tgaagttgaa 480
cagctgagaa gtggacccca agtcattcat tctggaatca aagacctcaa gctcttgaaa 540
acaacacagt ctggatttga aggtttcatc aaggaccagt tcactaccct ccctgaggtt 600
tttaaatgca tgatgagaac gttacctcag tcttctttcc ctttatttca agtgctctcc 660
atgggcagca gcctgatgga caccattcgg gaccttgtca tggagaaatc tgctgggccc 720
tatgacaaag atgaatactc gccctctgtg cagaagaccc tctgtgatat ccaggtgctc 780
tccctgagcc gagttcctgc gatagaagat atggaaatca gcctgccaaa cattcactac 840
ttcaacatag acatgtccaa aatgggtctg atcaacaagg aagaggtctt gctgccatta 900
gacaatccat atggaaaaat tactggtaca gtcaagagga agttgtcttc aagactgtga 960

<210> 312
<211> 927
<212> DNA
<213> Papio hamadryas

<220>

<221> misc_feature
<222> (927)
<223> n equals a,t,g, or c

<400> 312
```
atggccgact accataacaa ctataaaaag aatgatgaat tggagtttgt ccgaactggc     60
tatgggaagg atatggtaaa agttctccat attcagcgag atggaaaata tcacagcatt    120
aaagaggtgg caacttcagt gcaacttact ctgagttcca aaaaagatta cctgcatgga    180
gataattcag atatcatccc tacagacacc atcaagaaca cagttcatgt cttggcaaag    240
tttaagggaa tcaaaagcat agaagccttt ggtgtgaata tttgtgagta ttttctttct    300
tcttttaacc atgtaatccg agctcaagtc tacgtggaag aaatcccttg gaagcgtctt    360
gaaaagaatg gagttaagca tgtccatgca tttattcaca ctcccactgg aacacacttc    420
tgtgaagttg aacaactgag aagtggaccc cccgtcatta cttctggaat caaagacctc    480
aaggtcttga aaacaacaca gtctggattt gaaggtttca tcaaggacca gttcaccacc    540
ctccctgagg tgaaggaccg atgctttgcc acccaagtgt actgcaagtg gcgctaccac    600
cagtgcaggg atgtggactt cgaggctacc tggggcacca ttcgggacct tgtcctggag    660
aaatttgctg ggccctatga caaaggcgag tactcaccct ctgtgcagaa gaccctctat    720
gatatccagg tgctctccct gagccgagtt cctgagatag aagatatgga aatcagcctg    780
ccaaacattc actacttcaa tatagacatg tccaaaatgg gtctgatcaa caaggaagag    840
gtcttgctgc cattagacaa tccatatgga aaaattactg gtacagtcaa gaggaagttg    900
tcttcaagac tgtgacattg tggccan                                        927
```

<210> 313
<211> 805
<212> PRT
<213> Homo sapiens

<400> 313
```
Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1               5                   10                  15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg Asp Ala His
            20                  25                  30

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
        35                  40                  45

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
    50                  55                  60

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
65                  70                  75                  80

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
                85                  90                  95

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
            100                 105                 110

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
        115                 120                 125

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
    130                 135                 140

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
145                 150                 155                 160

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
                165                 170                 175
```

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
180 185 190

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
195 200 205

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
210 215 220

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
225 230 235 240

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
245 250 255

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
260 265 270

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
275 280 285

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
290 295 300

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
305 310 315 320

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
325 330 335

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
340 345 350

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
355 360 365

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
370 375 380

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
385 390 395 400

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
405 410 415

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
420 425 430

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
435 440 445

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
450 455 460

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
465 470 475 480

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
485 490 495

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn

500 505 510

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
515 520 525

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
530 535 540

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
545 550 555 560

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
565 570 575

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
580 585 590

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
595 600 605

Gln Ala Ala Leu Gly Leu Phe Pro Thr Ile Pro Leu Ser Arg Leu Phe
610 615 620

Asp Asn Ala Met Leu Arg Ala His Arg Leu His Gln Leu Ala Phe Asp
625 630 635 640

Thr Tyr Gln Glu Phe Glu Glu Ala Tyr Ile Pro Lys Glu Gln Lys Tyr
645 650 655

Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu Cys Phe Ser Glu Ser Ile
660 665 670

Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu
675 680 685

Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser Trp Leu Glu Pro Val
690 695 700

Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser
705 710 715 720

Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln
725 730 735

Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile
740 745 750

Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp
755 760 765

Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met
770 775 780

Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu
785 790 795 800

Gly Ser Cys Gly Phe
805

<210> 314
<211> 795
<212> PRT
<213> Homo sapiens

<400> 314
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
20 25 30

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
35 40 45

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
50 55 60

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
65 70 75 80

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
85 90 95

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
100 105 110

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
115 120 125

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
130 135 140

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
145 150 155 160

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
165 170 175

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
180 185 190

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
195 200 205

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
210 215 220

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
225 230 235 240

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
245 250 255

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
260 265 270

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
275 280 285

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu

290 295 300

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
305 310 315 320

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
325 330 335

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
340 345 350

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
355 360 365

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
370 375 380

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
385 390 395 400

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
405 410 415

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
420 425 430

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
435 440 445

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
450 455 460

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
465 470 475 480

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
485 490 495

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
500 505 510

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
515 520 525

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
530 535 540

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
545 550 555 560

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
565 570 575

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
580 585 590

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Phe Pro Thr Ile
595 600 605

Pro Leu Ser Arg Leu Phe Asp Asn Ala Met Leu Arg Ala His Arg Leu
610 615 620

His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala Tyr Ile
625 630 635 640

Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu
645 650 655

Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln
660 665 670

Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln
675 680 685

Ser Trp Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser
690 695 700

Leu Val Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp
705 710 715 720

Leu Glu Glu Gly Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser
725 730 735

Pro Arg Thr Gly Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr
740 745 750

Asn Ser His Asn Asp Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr
755 760 765

Cys Phe Arg Lys Asp Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val
770 775 780

Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
785 790 795

<210> 315
<211> 793
<212> PRT
<213> Homo sapiens

<400> 315
Met Phe Lys Ser Val Val Tyr Ser Ile Leu Ala Ala Ser Leu Ala Asn
1 5 10 15

Ala Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
20 25 30

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
35 40 45

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
50 55 60

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
65 70 75 80

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
85 90 95

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu

```
                100                 105                 110

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
        115                 120                 125

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
    130                 135                 140

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
145                 150                 155                 160

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
                165                 170                 175

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
            180                 185                 190

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
        195                 200                 205

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
    210                 215                 220

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
225                 230                 235                 240

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
                245                 250                 255

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
            260                 265                 270

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
        275                 280                 285

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
    290                 295                 300

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
305                 310                 315                 320

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
                325                 330                 335

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
            340                 345                 350

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
        355                 360                 365

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
    370                 375                 380

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
385                 390                 395                 400

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
                405                 410                 415

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
            420                 425                 430
```

```
Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
        435                 440                 445

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
    450                 455                 460

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
465                 470                 475                 480

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
                485                 490                 495

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
            500                 505                 510

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
        515                 520                 525

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
    530                 535                 540

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
545                 550                 555                 560

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
                565                 570                 575

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
            580                 585                 590

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Phe Pro Thr Ile Pro Leu
        595                 600                 605

Ser Arg Leu Phe Asp Asn Ala Met Leu Arg Ala His Arg Leu His Gln
    610                 615                 620

Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala Tyr Ile Pro Lys
625                 630                 635                 640

Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu Cys Phe
                645                 650                 655

Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln Gln Lys
            660                 665                 670

Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser Trp
        675                 680                 685

Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val
    690                 695                 700

Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu
705                 710                 715                 720

Glu Gly Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg
                725                 730                 735

Thr Gly Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser
            740                 745                 750
```

His Asn Asp Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe
        755   760   765

Arg Lys Asp Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys
    770   775   780

Arg Ser Val Glu Gly Ser Cys Gly Phe
785   790

<210> 316
<211> 800
<212> PRT
<213> Homo sapiens

<400> 316
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser Gly Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20   25   30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35   40   45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50   55   60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65   70   75   80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85   90   95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100   105   110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115   120   125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130   135   140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145   150   155   160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165   170   175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180   185   190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195   200   205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210   215   220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225   230   235   240

```
Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560
```

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Phe Pro Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Met Leu
610 615 620

Arg Ala His Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe
625 630 635 640

Glu Glu Ala Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn
645 650 655

Pro Gln Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn
660 665 670

Arg Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser
675 680 685

Leu Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg Ser
690 695 700

Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn Val Tyr
705 710 715 720

Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu Met Gly Arg
725 730 735

Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe Lys Gln Thr Tyr
740 745 750

Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp Ala Leu Leu Lys Asn
755 760 765

Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met Asp Lys Val Glu Thr
770 775 780

Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
785 790 795 800

<210> 317
<211> 774
<212> PRT
<213> Homo sapiens

<400> 317
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Gly Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

```
Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365
```

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu

```
690                 695                 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705                 710                 715                 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
                725                 730                 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
            740                 745                 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
        755                 760                 765

Ser Leu Arg Ser Lys Glu
    770


<210> 318
<211> 728
<212> PRT
<213> Homo sapiens

<400> 318
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg His Ser Asp Pro Ala Arg Arg Gly
            20                  25                  30

Glu Leu Ser Val Cys Asp Ser Ile Ser Glu Trp Val Thr Ala Ala Asp
        35                  40                  45

Lys Lys Thr Ala Val Asp Met Ser Gly Gly Thr Val Thr Val Leu Glu
    50                  55                  60

Lys Val Pro Val Ser Lys Gly Gln Leu Lys Gln Tyr Phe Tyr Glu Thr
65                  70                  75                  80

Lys Cys Asn Pro Met Gly Tyr Thr Lys Glu Gly Cys Arg Gly Ile Asp
                85                  90                  95

Lys Arg His Trp Asn Ser Gln Cys Arg Thr Thr Gln Ser Tyr Val Arg
            100                 105                 110

Ala Leu Thr Met Asp Ser Lys Lys Arg Ile Gly Trp Arg Phe Ile Arg
        115                 120                 125

Ile Asp Thr Ser Cys Val Cys Thr Leu Thr Ile Lys Arg Gly Arg Asp
    130                 135                 140

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
145                 150                 155                 160

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
                165                 170                 175

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
            180                 185                 190
```

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
195 200 205

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
210 215 220

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
225 230 235 240

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
245 250 255

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
260 265 270

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
275 280 285

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
290 295 300

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
305 310 315 320

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
325 330 335

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
340 345 350

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
355 360 365

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
370 375 380

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
385 390 395 400

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
405 410 415

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
420 425 430

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
435 440 445

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
450 455 460

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
465 470 475 480

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
485 490 495

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
500 505 510

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln

515 520 525

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
530 535 540

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
545 550 555 560

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
565 570 575

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
580 585 590

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
595 600 605

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
610 615 620

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
625 630 635 640

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
645 650 655

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
660 665 670

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
675 680 685

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
690 695 700

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
705 710 715 720

Ala Ser Gln Ala Ala Leu Gly Leu
725

<210> 319
<211> 669
<212> PRT
<213> Homo sapiens

<400> 319
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Gly Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser
20 25 30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
35 40 45

Trp Leu Val Lys Gly Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val
50 55 60

Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu

65 70 75 80

Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
85 90 95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
100 105 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
115 120 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
130 135 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145 150 155 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
165 170 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
180 185 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
195 200 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
210 215 220

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225 230 235 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
245 250 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
260 265 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
275 280 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
290 295 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305 310 315 320

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
325 330 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
340 345 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
355 360 365

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
370 375 380

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385 390 395 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
405 410 415

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
420 425 430

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
435 440 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
450 455 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465 470 475 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
485 490 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
500 505 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
515 520 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
530 535 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545 550 555 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
565 570 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
580 585 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
595 600 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
610 615 620

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
625 630 635 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
645 650 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 320
<211> 638
<212> PRT
<213> Homo sapiens

<400> 320
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala

1 5 10 15

Leu Gly Ser Gln Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
165 170 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
180 185 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
195 200 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
210 215 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225 230 235 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
245 250 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
260 265 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
275 280 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
290 295 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305 310 315 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
325 330 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
340 345 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
355 360 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
370 375 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385 390 395 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
405 410 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
420 425 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
435 440 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
450 455 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465 470 475 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
485 490 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
500 505 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 321

<211> 638
<212> PRT
<213> Homo sapiens

<400> 321
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
165 170 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
180 185 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
195 200 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
210 215 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225 230 235 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
245 250 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
260 265 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
275 280 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
290 295 300

```
Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305                 310                 315                 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                325                 330                 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
            340                 345                 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        355                 360                 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370                 375                 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385                 390                 395                 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                405                 410                 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
            420                 425                 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
        435                 440                 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
    450                 455                 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465                 470                 475                 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
                485                 490                 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
            500                 505                 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
        515                 520                 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
    530                 535                 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545                 550                 555                 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
                565                 570                 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
            580                 585                 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
        595                 600                 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
    610                 615                 620
```

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 322
<211> 666
<212> PRT
<213> Homo sapiens

<400> 322
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser
20 25 30

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
35 40 45

Lys Gly Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr
50 55 60

Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly
65 70 75 80

Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
85 90 95

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
100 105 110

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
115 120 125

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
130 135 140

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
145 150 155 160

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
165 170 175

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
180 185 190

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
195 200 205

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
210 215 220

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
225 230 235 240

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
245 250 255

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
260 265 270

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
275 280 285

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
290 295 300

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
305 310 315 320

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
325 330 335

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
340 345 350

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
355 360 365

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
370 375 380

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
385 390 395 400

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
405 410 415

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
420 425 430

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
435 440 445

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
450 455 460

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
465 470 475 480

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
485 490 495

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
500 505 510

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
515 520 525

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
530 535 540

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
545 550 555 560

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
565 570 575

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
580 585 590

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
595 600 605

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
610 615 620

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
625 630 635 640

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
645 650 655

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 323
<211> 574
<212> PRT
<213> Homo sapiens

<400> 323
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
50 55 60

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
65 70 75 80

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
85 90 95

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
100 105 110

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
115 120 125

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
130 135 140

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
145 150 155 160

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
165 170 175

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
180 185 190

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
195 200 205

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
210 215 220

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
225 230 235 240

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
245 250 255

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
260 265 270

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
275 280 285

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
290 295 300

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
305 310 315 320

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
325 330 335

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
340 345 350

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
355 360 365

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
370 375 380

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
385 390 395 400

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
405 410 415

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
420 425 430

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
435 440 445

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
450 455 460

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
465 470 475 480

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
485 490 495

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
500 505 510

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
515 520 525

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
530 535 540

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
545 550 555 560

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
565 570

<210> 324
<211> 638
<212> PRT
<213> Homo sapiens

<400> 324
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
165 170 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
180 185 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
195 200 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
210 215 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225 230 235 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
245 250 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
260 265 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
275 280 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
290 295 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305 310 315 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
325 330 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
340 345 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
355 360 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
370 375 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385 390 395 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
405 410 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
420 425 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
435 440 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
450 455 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465 470 475 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
485 490 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
500 505 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 325
<211> 638
<212> PRT
<213> Homo sapiens

<400> 325
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
165 170 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
180 185 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
195 200 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
210 215 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225 230 235 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
245 250 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
260 265 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
275 280 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
290 295 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305 310 315 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
325 330 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
340 345 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
355 360 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
370 375 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385 390 395 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
405 410 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
420 425 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
435 440 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
450 455 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465 470 475 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
485 490 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
500 505 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 326
<211> 640
<212> PRT
<213> Homo sapiens

<400> 326
Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1 5 10 15

Leu Trp Ala Pro Ala Arg Gly Ser Pro Lys Met Val Gln Gly Ser Gly
20 25 30

Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly
35 40 45

Cys Lys Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His
50 55 60

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
65 70 75 80

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
85 90 95

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
100 105 110

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
115 120 125

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
130 135 140

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
145 150 155 160

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
165 170 175

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
180 185 190

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
195 200 205

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
210 215 220

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
225 230 235 240

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
245 250 255

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
260 265 270

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
275 280 285

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
290 295 300

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
305 310 315 320

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
325 330 335

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
340 345 350

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
355 360 365

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
370 375 380

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
385 390 395 400

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
405 410 415

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
420 425 430

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
435 440 445

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
450 455 460

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
465 470 475 480

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
485 490 495

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
500 505 510

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
515 520 525

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
530 535 540

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
545 550 555 560

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
565 570 575

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
580 585 590

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
595 600 605

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
610 615 620

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635 640

<210> 327
<211> 640
<212> PRT
<213> Homo sapiens

<400> 327
Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1 5 10 15

Leu Trp Ala Pro Ala Arg Gly Ser Pro Lys Met Val Gln Gly Ser Gly
20 25 30

Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly
35 40 45

Cys Lys Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His
50 55 60

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
65 70 75 80

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
85 90 95

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
100 105 110

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
115 120 125

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
130 135 140

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
145 150 155 160

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
165 170 175

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
180 185 190

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
195 200 205

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
210 215 220

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
225 230 235 240

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
245 250 255

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
260 265 270

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
275 280 285

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
290 295 300

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
305 310 315 320

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
325 330 335

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
340 345 350

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
355 360 365

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
370 375 380

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
385 390 395 400

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
405 410 415

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
420 425 430

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
435 440 445

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
450 455 460

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu

465 470 475 480

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
485 490 495

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
500 505 510

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
515 520 525

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
530 535 540

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
545 550 555 560

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
565 570 575

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
580 585 590

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
595 600 605

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
610 615 620

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635 640

<210> 328
<211> 638
<212> PRT
<213> Homo sapiens

<400> 328
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Gly Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys

115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
165 170 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
180 185 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
195 200 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
210 215 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225 230 235 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
245 250 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
260 265 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
275 280 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
290 295 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305 310 315 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
325 330 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
340 345 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
355 360 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
370 375 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385 390 395 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
405 410 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
420 425 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
435 440 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
450 455 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465 470 475 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
485 490 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
500 505 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 329
<211> 571
<212> PRT
<213> Homo sapiens

<400> 329
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
50 55 60

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
65 70 75 80

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
85 90 95

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
100 105 110

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
115 120 125

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
130 135 140

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
145 150 155 160

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
165 170 175

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
180 185 190

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
195 200 205

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
210 215 220

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
225 230 235 240

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
245 250 255

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
260 265 270

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
275 280 285

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
290 295 300

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
305 310 315 320

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
325 330 335

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
340 345 350

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
355 360 365

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
370 375 380

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
385 390 395 400

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
405 410 415

```
Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
            420                 425                 430

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
        435                 440                 445

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
    450                 455                 460

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
465                 470                 475                 480

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
                485                 490                 495

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
            500                 505                 510

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
        515                 520                 525

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
    530                 535                 540

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
545                 550                 555                 560

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                565                 570


&lt;210&gt; 330
&lt;211&gt; 638
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 330
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1               5                   10                  15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
            20                  25                  30

Gly Gly Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
        35                  40                  45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
    50                  55                  60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65                  70                  75                  80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
                85                  90                  95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
            100                 105                 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
        115                 120                 125
```

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
165 170 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
180 185 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
195 200 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
210 215 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225 230 235 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
245 250 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
260 265 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
275 280 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
290 295 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305 310 315 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
325 330 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
340 345 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
355 360 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
370 375 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385 390 395 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
405 410 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
420 425 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
435 440 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
450 455 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465 470 475 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
485 490 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
500 505 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 331
<211> 638
<212> PRT
<213> Homo sapiens

<400> 331
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Gly Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
165 170 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
180 185 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
195 200 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
210 215 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225 230 235 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
245 250 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
260 265 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
275 280 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
290 295 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305 310 315 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
325 330 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
340 345 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
355 360 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
370 375 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385 390 395 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
405 410 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
420 425 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
435 440 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
450 455 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465 470 475 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
485 490 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
500 505 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 332
<211> 641
<212> PRT
<213> Homo sapiens

<400> 332
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu

```
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
    610                 615                 620

Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg
625                 630                 635                 640

His


<210> 333
<211> 642
<212> PRT
<213> Homo sapiens

<400> 333
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
```

20 25 30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Arg Gly Gly Gly Asp Ala His Lys Ser Glu Val
50 55 60

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
65 70 75 80

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
85 90 95

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
100 105 110

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
115 120 125

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
130 135 140

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
145 150 155 160

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
165 170 175

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
180 185 190

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
195 200 205

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
210 215 220

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
225 230 235 240

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
245 250 255

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
260 265 270

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
275 280 285

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
290 295 300

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
305 310 315 320

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
325 330 335

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
340 345 350

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
355 360 365

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
370 375 380

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
385 390 395 400

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
405 410 415

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
420 425 430

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
435 440 445

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
450 455 460

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
465 470 475 480

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
485 490 495

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
500 505 510

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
515 520 525

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
530 535 540

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
545 550 555 560

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
565 570 575

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
580 585 590

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
595 600 605

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
610 615 620

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
625 630 635 640

Gly Leu

<210> 334

<211> 639
<212> PRT
<213> Homo sapiens

<400> 334
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser Arg Ser Leu Asp Lys Arg Asn Pro Met Tyr Asn Ala Val Ser
            20   25   30

Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu Glu
        35   40   45

Lys Met Pro Leu Glu Asp Asp Ala His Lys Ser Glu Val Ala His Arg
    50   55   60

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65   70   75   80

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
                85   90   95

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
            100   105   110

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
        115   120   125

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
    130   135   140

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
145   150   155   160

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
                165   170   175

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            180   185   190

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        195   200   205

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    210   215   220

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
225   230   235   240

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                245   250   255

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            260   265   270

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        275   280   285

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    290   295   300

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
305 310 315 320

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
325 330 335

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
340 345 350

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
355 360 365

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
370 375 380

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
385 390 395 400

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
405 410 415

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
420 425 430

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
435 440 445

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
450 455 460

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
465 470 475 480

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
485 490 495

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
500 505 510

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
515 520 525

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
530 535 540

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
545 550 555 560

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
565 570 575

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
580 585 590

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
595 600 605

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
610 615 620

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 335
<211> 639
<212> PRT
<213> Homo sapiens

<400> 335
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Asn Pro Met Tyr Asn Ala Val Ser Asn Ala Asp Leu Met Asp Phe
610 615 620

Lys Asn Leu Leu Asp His Leu Glu Glu Lys Met Pro Leu Glu Asp
625 630 635

<210> 336
<211> 646
<212> PRT
<213> Homo sapiens

<400> 336
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Glu Val Val Pro Pro Gln Val Leu
20 25 30

Ser Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu
35 40 45

Val Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Ala His
50 55 60

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
65 70 75 80

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
85 90 95

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
100 105 110

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
115 120 125

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
130 135 140

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
145 150 155 160

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
165 170 175

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
180 185 190

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
195 200 205

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
210 215 220

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
225 230 235 240

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
245 250 255

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
260 265 270

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
275 280 285

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
290 295 300

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
305 310 315 320

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
325 330 335

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
340 345 350

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
355 360 365

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
370 375 380

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
385 390 395 400

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
405 410 415

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
420 425 430

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
435 440 445

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
450 455 460

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
465 470 475 480

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
485 490 495

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
500 505 510

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
515 520 525

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
530 535 540

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
545 550 555 560

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
565 570 575

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
580 585 590

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
595 600 605

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
610 615 620

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
625 630 635 640

Gln Ala Ala Leu Gly Leu
645

<210> 337
<211> 646
<212> PRT
<213> Homo sapiens

<400> 337
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Glu Val Val Pro Pro Gln Val Leu Ser Glu Pro Asn Glu Glu Ala
610 615 620

Gly Ala Ala Leu Ser Pro Leu Pro Glu Val Pro Pro Trp Thr Gly Glu
625 630 635 640

Val Ser Pro Ala Gln Arg
645

<210> 338
<211> 629
<212> PRT
<213> Homo sapiens

<400> 338
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Ser Asp Arg Ser Ala Leu Leu
20 25 30

Lys Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Asp Ala His Lys
35 40 45

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
50 55 60

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
65 70 75 80

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
85 90 95

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
100 105 110

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
115 120 125

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
130 135 140

```
Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
145                 150                 155                 160

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
                165                 170                 175

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
            180                 185                 190

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
        195                 200                 205

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
    210                 215                 220

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
225                 230                 235                 240

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
                245                 250                 255

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
            260                 265                 270

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
        275                 280                 285

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
    290                 295                 300

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
305                 310                 315                 320

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
                325                 330                 335

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
            340                 345                 350

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
        355                 360                 365

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
    370                 375                 380

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
385                 390                 395                 400

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
                405                 410                 415

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
            420                 425                 430

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
        435                 440                 445

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
    450                 455                 460
```

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
465 470 475 480

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
485 490 495

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
500 505 510

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
515 520 525

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
530 535 540

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
545 550 555 560

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
565 570 575

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
580 585 590

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
595 600 605

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
610 615 620

Ala Ala Leu Gly Leu
625

<210> 339
<211> 629
<212> PRT
<213> Homo sapiens

<400> 339
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ser Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu
610 615 620

Leu Thr Ala Pro Arg
625

<210> 340
<211> 631
<212> PRT
<213> Homo sapiens

<400> 340
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Leu Ser Lys Gly Cys Phe Gly
20 25 30

Leu Lys Leu Asp Arg Ile Gly Ser Met Ser Gly Leu Gly Cys Asp Ala
35 40 45

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
50 55 60

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
65 70 75 80

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
85 90 95

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
100 105 110

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
115 120 125

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
130 135 140

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
145 150 155 160

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
165 170 175

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
180 185 190

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
195 200 205

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
210 215 220

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
225 230 235 240

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
245 250 255

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
260 265 270

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
275 280 285

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
290 295 300

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
305 310 315 320

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
325 330 335

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
340 345 350

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
355 360 365

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
370 375 380

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
385 390 395 400

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
405 410 415

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
420 425 430

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
435 440 445

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
450 455 460

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
465 470 475 480

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
485 490 495

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
500 505 510

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
515 520 525

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
530 535 540

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
545 550 555 560

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
565 570 575

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
580 585 590

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
595 600 605

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
610 615 620

Ser Gln Ala Ala Leu Gly Leu
625 630

<210> 341
<211> 631
<212> PRT
<213> Homo sapiens

<400> 341
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

```
Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365
```

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370   375   380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385   390   395   400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405   410   415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420   425   430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435   440   445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450   455   460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465   470   475   480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485   490   495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500   505   510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515   520   525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530   535   540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545   550   555   560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565   570   575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580   585   590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595   600   605

Leu Gly Leu Ser Lys Gly Cys Phe Gly Leu Lys Leu Asp Arg Ile Gly
    610   615   620

Ser Met Ser Gly Leu Gly Cys
625   630

<210> 342
<211> 647
<212> PRT
<213> Homo sapiens

<400> 342
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser Arg Ser Leu Asp Lys Arg Glu Val Lys Tyr Asp Pro Cys Phe
20 25 30

Gly His Lys Ile Asp Arg Ile Asn His Val Ser Asn Leu Gly Cys Pro
35 40 45

Ser Leu Arg Asp Pro Arg Pro Asn Ala Pro Ser Thr Ser Ala Asp Ala
50 55 60

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
65 70 75 80

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
85 90 95

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
100 105 110

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
115 120 125

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
130 135 140

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
145 150 155 160

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
165 170 175

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
180 185 190

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
195 200 205

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
210 215 220

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
225 230 235 240

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
245 250 255

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
260 265 270

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
275 280 285

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
290 295 300

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
305 310 315 320

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
325 330 335

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
340 345 350

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
355 360 365

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
370 375 380

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
385 390 395 400

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
405 410 415

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
420 425 430

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
435 440 445

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
450 455 460

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
465 470 475 480

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
485 490 495

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
500 505 510

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
515 520 525

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
530 535 540

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
545 550 555 560

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
565 570 575

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
580 585 590

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
595 600 605

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
610 615 620

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
625 630 635 640

Ser Gln Ala Ala Leu Gly Leu
645

<210> 343
<211> 647
<212> PRT
<213> Homo sapiens

<400> 343
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20   25   30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35   40   45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50   55   60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65   70   75   80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85   90   95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100   105   110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115   120   125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130   135   140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145   150   155   160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165   170   175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180   185   190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195   200   205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210   215   220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225   230   235   240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245   250   255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260   265   270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275   280   285

```
Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Glu Val Lys Tyr Asp Pro Cys Phe Gly His Lys Ile Asp Arg Ile
```

610 615 620

Asn His Val Ser Asn Leu Gly Cys Pro Ser Leu Arg Asp Pro Arg Pro
625 630 635 640

Asn Ala Pro Ser Thr Ser Ala
645

<210> 344
<211> 642
<212> PRT
<213> Homo sapiens

<400> 344
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Gly Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Arg Gly Gly Gly Asp Ala His Lys Ser Glu Val
50 55 60

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
65 70 75 80

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
85 90 95

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
100 105 110

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
115 120 125

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
130 135 140

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
145 150 155 160

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
165 170 175

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
180 185 190

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
195 200 205

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
210 215 220

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
225 230 235 240

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
245 250 255

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
260 265 270

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
275 280 285

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
290 295 300

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
305 310 315 320

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
325 330 335

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
340 345 350

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
355 360 365

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
370 375 380

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
385 390 395 400

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
405 410 415

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
420 425 430

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
435 440 445

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
450 455 460

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
465 470 475 480

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
485 490 495

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
500 505 510

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
515 520 525

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
530 535 540

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
545 550 555 560

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys

565 570 575

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
580 585 590

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
595 600 605

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
610 615 620

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
625 630 635 640

Gly Leu

<210> 345
<211> 638
<212> PRT
<213> Homo sapiens

<400> 345
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Gly Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
165 170 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
180 185 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
195 200 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
    210   215   220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225   230   235   240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                245   250   255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            260   265   270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        275   280   285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    290   295   300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305   310   315   320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                325   330   335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
            340   345   350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        355   360   365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370   375   380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385   390   395   400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                405   410   415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
            420   425   430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
        435   440   445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
    450   455   460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465   470   475   480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
                485   490   495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
            500   505   510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
        515   520   525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 346
<211> 641
<212> PRT
<213> Homo sapiens

<400> 346
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Gly Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala
50 55 60

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
65 70 75 80

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
85 90 95

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
100 105 110

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
115 120 125

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
130 135 140

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
145 150 155 160

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
165 170 175

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
180 185 190

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
195 200 205

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
210 215 220

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
225 230 235 240

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
245 250 255

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
260 265 270

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
275 280 285

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
290 295 300

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
305 310 315 320

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
325 330 335

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
340 345 350

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
355 360 365

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
370 375 380

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
385 390 395 400

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
405 410 415

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
420 425 430

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
435 440 445

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
450 455 460

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
465 470 475 480

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
485 490 495

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
500 505 510

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
515 520 525

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
530 535 540

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
545 550 555 560

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
565 570 575

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
580 585 590

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
595 600 605

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
610 615 620

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
625 630 635 640

Leu

<210> 347
<211> 641
<212> PRT
<213> Homo sapiens

<400> 347
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Gly Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Gly Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala
50 55 60

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
65 70 75 80

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
85 90 95

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
100 105 110

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
115 120 125

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala

130 135 140

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
145 150 155 160

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
165 170 175

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
180 185 190

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
195 200 205

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
210 215 220

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
225 230 235 240

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
245 250 255

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
260 265 270

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
275 280 285

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
290 295 300

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
305 310 315 320

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
325 330 335

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
340 345 350

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
355 360 365

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
370 375 380

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
385 390 395 400

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
405 410 415

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
420 425 430

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
435 440 445

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
450 455 460

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
465 470 475 480

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
485 490 495

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
500 505 510

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
515 520 525

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
530 535 540

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
545 550 555 560

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
565 570 575

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
580 585 590

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
595 600 605

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
610 615 620

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
625 630 635 640

Leu

<210> 348
<211> 641
<212> PRT
<213> Homo sapiens

<400> 348
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp

85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

```
Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Gly Met
    610                 615                 620

Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg
625                 630                 635                 640

His


<210> 349
<211> 909
<212> PRT
<213> Homo sapiens

<400> 349
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1               5                   10                  15

Pro Met Val Trp Ala Met Ala His Tyr His Asp Asp Tyr Gly Lys Asn
            20                  25                  30

Asp Glu Val Glu Phe Val Arg Thr Gly Tyr Gly Lys Asp Met Val Lys
        35                  40                  45
```

Val Leu His Ile Gln Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val
50 55 60

Ala Thr Ser Val Gln Leu Thr Leu Arg Ser Lys Lys Asp Tyr Leu His
65 70 75 80

Gly Asp Asn Ser Asp Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val
85 90 95

His Val Leu Ala Lys Phe Lys Gly Ile Lys Ser Ile Glu Thr Phe Ala
100 105 110

Met Asn Ile Cys Glu His Phe Leu Ser Ser Phe Ser His Val Thr Arg
115 120 125

Ala His Val Tyr Val Glu Glu Val Pro Trp Lys Arg Phe Glu Lys Asn
130 135 140

Gly Val Lys His Val His Ala Phe Ile His Thr Pro Thr Gly Thr His
145 150 155 160

Phe Cys Asp Val Glu Gln Val Arg Asn Gly Pro Pro Ile Ile His Ser
165 170 175

Gly Ile Lys Asp Leu Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu
180 185 190

Gly Phe Ile Lys Asp Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg
195 200 205

Cys Phe Ala Thr Gln Val Tyr Cys Lys Trp Arg Tyr Gln Asn Arg Asp
210 215 220

Val Asp Phe Glu Ala Thr Trp Gly Ala Val Arg Asp Ile Val Leu Lys
225 230 235 240

Lys Phe Ala Gly Pro Tyr Asp Arg Gly Glu Tyr Ser Pro Ser Val Gln
245 250 255

Lys Thr Leu Tyr Asp Ile Gln Val Leu Thr Leu Ser Gln Leu Pro Glu
260 265 270

Ile Glu Asp Met Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile
275 280 285

Asp Met Ser Lys Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro
290 295 300

Leu Asp Asn Pro Tyr Gly Lys Ile Thr Gly Thr Val Arg Arg Lys Leu
305 310 315 320

Pro Ser Arg Leu Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
325 330 335

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
340 345 350

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
355 360 365

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
370 375 380

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
385 390 395 400

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
405 410 415

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
420 425 430

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
435 440 445

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
450 455 460

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
465 470 475 480

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
485 490 495

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
500 505 510

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
515 520 525

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
530 535 540

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
545 550 555 560

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
565 570 575

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
580 585 590

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
595 600 605

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
610 615 620

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
625 630 635 640

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
645 650 655

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
660 665 670

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
675 680 685

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu

690 695 700

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
705 710 715 720

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
725 730 735

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
740 745 750

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
755 760 765

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
770 775 780

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
785 790 795 800

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
805 810 815

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
820 825 830

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
835 840 845

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
850 855 860

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
865 870 875 880

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
885 890 895

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
900 905

<210> 350
<211> 912
<212> PRT
<213> Homo sapiens

<400> 350
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp

65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

```
Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Met Ala His Tyr His Asp Asp Tyr Gly Lys Asn Asp Glu Val Glu
    610                 615                 620

Phe Val Arg Thr Gly Tyr Gly Lys Asp Met Val Lys Val Leu His Ile
625                 630                 635                 640

Gln Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val
                645                 650                 655

Gln Leu Thr Leu Arg Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser
            660                 665                 670

Asp Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala
        675                 680                 685

Lys Phe Lys Gly Ile Lys Ser Ile Glu Thr Phe Ala Met Asn Ile Cys
    690                 695                 700

Glu His Phe Leu Ser Ser Phe Ser His Val Thr Arg Ala His Val Tyr
705                 710                 715                 720
```

Val Glu Glu Val Pro Trp Lys Arg Phe Glu Lys Asn Gly Val Lys His
725 730 735

Val His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Asp Val
740 745 750

Glu Gln Val Arg Asn Gly Pro Pro Ile Ile His Ser Gly Ile Lys Asp
755 760 765

Leu Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys
770 775 780

Asp Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr
785 790 795 800

Gln Val Tyr Cys Lys Trp Arg Tyr Gln Asn Arg Asp Val Asp Phe Glu
805 810 815

Ala Thr Trp Gly Ala Val Arg Asp Ile Val Leu Lys Lys Phe Ala Gly
820 825 830

Pro Tyr Asp Arg Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
835 840 845

Asp Ile Gln Val Leu Thr Leu Ser Gln Leu Pro Glu Ile Glu Asp Met
850 855 860

Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys
865 870 875 880

Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro
885 890 895

Tyr Gly Lys Ile Thr Gly Thr Val Arg Arg Lys Leu Pro Ser Arg Leu
900 905 910

<210> 351
<211> 1019
<212> PRT
<213> Homo sapiens

<400> 351
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Met Ser Val Phe Asp Ser Lys Phe
20 25 30

Lys Gly Ile His Val Tyr Ser Glu Ile Gly Glu Leu Glu Ser Val Leu
35 40 45

Val His Glu Pro Gly Arg Glu Ile Asp Tyr Ile Thr Pro Ala Arg Leu
50 55 60

Asp Glu Leu Leu Phe Ser Ala Ile Leu Glu Ser His Asp Ala Arg Lys
65 70 75 80

Glu His Lys Gln Phe Val Ala Glu Leu Lys Ala Asn Asp Ile Asn Val

```
                85                  90                  95

Val Glu Leu Ile Asp Leu Val Ala Glu Thr Tyr Asp Leu Ala Ser Gln
            100                 105                 110

Glu Ala Lys Asp Lys Leu Ile Glu Glu Phe Leu Glu Asp Ser Glu Pro
        115                 120                 125

Val Leu Ser Glu Glu His Lys Val Val Val Arg Asn Phe Leu Lys Ala
    130                 135                 140

Lys Lys Thr Ser Arg Lys Leu Val Glu Ile Met Met Ala Gly Ile Thr
145                 150                 155                 160

Lys Tyr Asp Leu Gly Ile Glu Ala Asp His Glu Leu Ile Val Asp Pro
                165                 170                 175

Met Pro Asn Leu Tyr Phe Thr Arg Asp Pro Phe Ala Ser Val Gly Asn
            180                 185                 190

Gly Val Thr Ile His Tyr Met Arg Tyr Lys Val Arg Gln Arg Glu Thr
        195                 200                 205

Leu Phe Ser Arg Phe Val Phe Ser Asn His Pro Lys Leu Ile Asn Thr
    210                 215                 220

Pro Trp Tyr Tyr Asp Pro Ser Leu Lys Leu Ser Ile Glu Gly Gly Asp
225                 230                 235                 240

Val Phe Ile Tyr Asn Asn Asp Thr Leu Val Val Gly Val Ser Glu Arg
                245                 250                 255

Thr Asp Leu Gln Thr Val Thr Leu Leu Ala Lys Asn Ile Val Ala Asn
            260                 265                 270

Lys Glu Cys Glu Phe Lys Arg Ile Val Ala Ile Asn Val Pro Lys Trp
        275                 280                 285

Thr Asn Leu Met His Leu Asp Thr Trp Leu Thr Met Leu Asp Lys Asp
    290                 295                 300

Lys Phe Leu Tyr Ser Pro Ile Ala Asn Asp Val Phe Lys Phe Trp Asp
305                 310                 315                 320

Tyr Asp Leu Val Asn Gly Gly Ala Glu Pro Gln Pro Val Glu Asn Gly
                325                 330                 335

Leu Pro Leu Glu Gly Leu Leu Gln Ser Ile Ile Asn Lys Lys Pro Val
            340                 345                 350

Leu Ile Pro Ile Ala Gly Glu Gly Ala Ser Gln Met Glu Ile Glu Arg
        355                 360                 365

Glu Thr His Phe Asp Gly Thr Asn Tyr Leu Ala Ile Arg Pro Gly Val
    370                 375                 380

Val Ile Gly Tyr Ser Arg Asn Glu Lys Thr Asn Ala Ala Leu Glu Ala
385                 390                 395                 400

Ala Gly Ile Lys Val Leu Pro Phe His Gly Asn Gln Leu Ser Leu Gly
                405                 410                 415
```

```
Met Gly Asn Ala Arg Cys Met Ser Met Pro Leu Ser Arg Lys Asp Val
            420                 425                 430

Lys Trp Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
        435                 440                 445

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
    450                 455                 460

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
465                 470                 475                 480

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
                485                 490                 495

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
            500                 505                 510

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
        515                 520                 525

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
    530                 535                 540

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
545                 550                 555                 560

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
                565                 570                 575

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
            580                 585                 590

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
        595                 600                 605

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
    610                 615                 620

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
625                 630                 635                 640

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
                645                 650                 655

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
            660                 665                 670

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
        675                 680                 685

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
    690                 695                 700

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
705                 710                 715                 720

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
                725                 730                 735
```

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
740 745 750

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
755 760 765

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
770 775 780

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
785 790 795 800

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
805 810 815

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
820 825 830

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
835 840 845

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
850 855 860

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
865 870 875 880

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
885 890 895

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
900 905 910

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
915 920 925

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
930 935 940

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
945 950 955 960

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
965 970 975

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
980 985 990

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
995 1000 1005

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
1010 1015

<210> 352
<211> 1016
<212> PRT
<213> Homo sapiens

<400> 352

Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1   5   10   15

Pro Met Val Trp Ala Met Ser Val Phe Asp Ser Lys Phe Lys Gly Ile
            20   25   30

His Val Tyr Ser Glu Ile Gly Glu Leu Glu Ser Val Leu Val His Glu
        35   40   45

Pro Gly Arg Glu Ile Asp Tyr Ile Thr Pro Ala Arg Leu Asp Glu Leu
    50   55   60

Leu Phe Ser Ala Ile Leu Glu Ser His Asp Ala Arg Lys Glu His Lys
65   70   75   80

Gln Phe Val Ala Glu Leu Lys Ala Asn Asp Ile Asn Val Val Glu Leu
                85   90   95

Ile Asp Leu Val Ala Glu Thr Tyr Asp Leu Ala Ser Gln Glu Ala Lys
            100   105   110

Asp Lys Leu Ile Glu Glu Phe Leu Glu Asp Ser Glu Pro Val Leu Ser
        115   120   125

Glu Glu His Lys Val Val Val Arg Asn Phe Leu Lys Ala Lys Lys Thr
    130   135   140

Ser Arg Lys Leu Val Glu Ile Met Met Ala Gly Ile Thr Lys Tyr Asp
145   150   155   160

Leu Gly Ile Glu Ala Asp His Glu Leu Ile Val Asp Pro Met Pro Asn
                165   170   175

Leu Tyr Phe Thr Arg Asp Pro Phe Ala Ser Val Gly Asn Gly Val Thr
            180   185   190

Ile His Tyr Met Arg Tyr Lys Val Arg Gln Arg Glu Thr Leu Phe Ser
        195   200   205

Arg Phe Val Phe Ser Asn His Pro Lys Leu Ile Asn Thr Pro Trp Tyr
    210   215   220

Tyr Asp Pro Ser Leu Lys Leu Ser Ile Glu Gly Gly Asp Val Phe Ile
225   230   235   240

Tyr Asn Asn Asp Thr Leu Val Val Gly Val Ser Glu Arg Thr Asp Leu
                245   250   255

Gln Thr Val Thr Leu Leu Ala Lys Asn Ile Val Ala Asn Lys Glu Cys
            260   265   270

Glu Phe Lys Arg Ile Val Ala Ile Asn Val Pro Lys Trp Thr Asn Leu
        275   280   285

Met His Leu Asp Thr Trp Leu Thr Met Leu Asp Lys Asp Lys Phe Leu
    290   295   300

Tyr Ser Pro Ile Ala Asn Asp Val Phe Lys Phe Trp Asp Tyr Asp Leu
305   310   315   320

Val Asn Gly Gly Ala Glu Pro Gln Pro Val Glu Asn Gly Leu Pro Leu
325 330 335

Glu Gly Leu Leu Gln Ser Ile Ile Asn Lys Lys Pro Val Leu Ile Pro
340 345 350

Ile Ala Gly Glu Gly Ala Ser Gln Met Glu Ile Glu Arg Glu Thr His
355 360 365

Phe Asp Gly Thr Asn Tyr Leu Ala Ile Arg Pro Gly Val Val Ile Gly
370 375 380

Tyr Ser Arg Asn Glu Lys Thr Asn Ala Ala Leu Glu Ala Ala Gly Ile
385 390 395 400

Lys Val Leu Pro Phe His Gly Asn Gln Leu Ser Leu Gly Met Gly Asn
405 410 415

Ala Arg Cys Met Ser Met Pro Leu Ser Arg Lys Asp Val Lys Trp Asp
420 425 430

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
435 440 445

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
450 455 460

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
465 470 475 480

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
485 490 495

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
500 505 510

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
515 520 525

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
530 535 540

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
545 550 555 560

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
565 570 575

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
580 585 590

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
595 600 605

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
610 615 620

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
625 630 635 640

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys

```
                645                 650                 655

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
            660                 665                 670

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
        675                 680                 685

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
    690                 695                 700

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
705                 710                 715                 720

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
                725                 730                 735

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
            740                 745                 750

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
        755                 760                 765

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
    770                 775                 780

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
785                 790                 795                 800

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
                805                 810                 815

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
            820                 825                 830

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
        835                 840                 845

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
    850                 855                 860

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
865                 870                 875                 880

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
                885                 890                 895

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
            900                 905                 910

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
        915                 920                 925

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
    930                 935                 940

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
945                 950                 955                 960

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
                965                 970                 975
```

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
980 985 990

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
995 1000 1005

Ala Ser Gln Ala Ala Leu Gly Leu
1010 1015

<210> 353
<211> 1019
<212> PRT
<213> Homo sapiens

<400> 353
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val

225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Ser Val Phe Asp Ser Lys Phe Lys Gly Ile His Val Tyr Ser
610 615 620

Glu Ile Gly Glu Leu Glu Ser Val Leu Val His Glu Pro Gly Arg Glu
625 630 635 640

Ile Asp Tyr Ile Thr Pro Ala Arg Leu Asp Glu Leu Leu Phe Ser Ala
645 650 655

Ile Leu Glu Ser His Asp Ala Arg Lys Glu His Lys Gln Phe Val Ala
660 665 670

Glu Leu Lys Ala Asn Asp Ile Asn Val Val Glu Leu Ile Asp Leu Val
675 680 685

Ala Glu Thr Tyr Asp Leu Ala Ser Gln Glu Ala Lys Asp Lys Leu Ile
690 695 700

Glu Glu Phe Leu Glu Asp Ser Glu Pro Val Leu Ser Glu Glu His Lys
705 710 715 720

Val Val Val Arg Asn Phe Leu Lys Ala Lys Lys Thr Ser Arg Lys Leu
725 730 735

Val Glu Ile Met Met Ala Gly Ile Thr Lys Tyr Asp Leu Gly Ile Glu
740 745 750

Ala Asp His Glu Leu Ile Val Asp Pro Met Pro Asn Leu Tyr Phe Thr
755 760 765

Arg Asp Pro Phe Ala Ser Val Gly Asn Gly Val Thr Ile His Tyr Met
770 775 780

Arg Tyr Lys Val Arg Gln Arg Glu Thr Leu Phe Ser Arg Phe Val Phe
785 790 795 800

Ser Asn His Pro Lys Leu Ile Asn Thr Pro Trp Tyr Tyr Asp Pro Ser
805 810 815

Leu Lys Leu Ser Ile Glu Gly Gly Asp Val Phe Ile Tyr Asn Asn Asp
820 825 830

Thr Leu Val Val Gly Val Ser Glu Arg Thr Asp Leu Gln Thr Val Thr
835 840 845

Leu Leu Ala Lys Asn Ile Val Ala Asn Lys Glu Cys Glu Phe Lys Arg
850 855 860

Ile Val Ala Ile Asn Val Pro Lys Trp Thr Asn Leu Met His Leu Asp
865 870 875 880

Thr Trp Leu Thr Met Leu Asp Lys Asp Lys Phe Leu Tyr Ser Pro Ile
885 890 895

Ala Asn Asp Val Phe Lys Phe Trp Asp Tyr Asp Leu Val Asn Gly Gly
900 905 910

Ala Glu Pro Gln Pro Val Glu Asn Gly Leu Pro Leu Glu Gly Leu Leu
915 920 925

Gln Ser Ile Ile Asn Lys Lys Pro Val Leu Ile Pro Ile Ala Gly Glu
930 935 940

Gly Ala Ser Gln Met Glu Ile Glu Arg Glu Thr His Phe Asp Gly Thr
945 950 955 960

Asn Tyr Leu Ala Ile Arg Pro Gly Val Val Ile Gly Tyr Ser Arg Asn
965 970 975

Glu Lys Thr Asn Ala Ala Leu Glu Ala Ala Gly Ile Lys Val Leu Pro
980 985 990

Phe His Gly Asn Gln Leu Ser Leu Gly Met Gly Asn Ala Arg Cys Met
995 1000 1005

Ser Met Pro Leu Ser Arg Lys Asp Val Lys Trp
1010 1015

<210> 354
<211> 1019
<212> PRT
<213> Homo sapiens

<400> 354
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Ser Val Phe Asp Ser Lys Phe Lys Gly Ile His Val Tyr Ser
610 615 620

Glu Ile Gly Glu Leu Glu Ser Val Leu Val His Glu Pro Gly Arg Glu
625 630 635 640

Ile Asp Tyr Ile Thr Pro Ala Arg Leu Asp Glu Leu Leu Phe Ser Ala
645 650 655

Ile Leu Glu Ser His Asp Ala Arg Lys Glu His Lys Gln Phe Val Ala
660 665 670

Glu Leu Lys Ala Asn Asp Ile Asn Val Val Glu Leu Ile Asp Leu Val
675 680 685

Ala Glu Thr Tyr Asp Leu Ala Ser Gln Glu Ala Lys Asp Lys Leu Ile
690 695 700

Glu Glu Phe Leu Glu Asp Ser Glu Pro Val Leu Ser Glu Glu His Lys
705 710 715 720

Val Val Val Arg Asn Phe Leu Lys Ala Lys Lys Thr Ser Arg Lys Leu
725 730 735

Val Glu Ile Met Met Ala Gly Ile Thr Lys Tyr Asp Leu Gly Ile Glu
740 745 750

Ala Asp His Glu Leu Ile Val Asp Pro Met Pro Asn Leu Tyr Phe Thr
755 760 765

Arg Asp Pro Phe Ala Ser Val Gly Asn Gly Val Thr Ile His Tyr Met
770 775 780

Arg Tyr Lys Val Arg Gln Arg Glu Thr Leu Phe Ser Arg Phe Val Phe

785 790 795 800

Ser Asn His Pro Lys Leu Ile Asn Thr Pro Trp Tyr Tyr Asp Pro Ser
805 810 815

Leu Lys Leu Ser Ile Glu Gly Gly Asp Val Phe Ile Tyr Asn Asn Asp
820 825 830

Thr Leu Val Val Gly Val Ser Glu Arg Thr Asp Leu Gln Thr Val Thr
835 840 845

Leu Leu Ala Lys Asn Ile Val Ala Asn Lys Glu Cys Glu Phe Lys Arg
850 855 860

Ile Val Ala Ile Asn Val Pro Lys Trp Thr Asn Leu Met His Leu Asp
865 870 875 880

Thr Trp Leu Thr Met Leu Asp Lys Asp Lys Phe Leu Tyr Ser Pro Ile
885 890 895

Ala Asn Asp Val Phe Lys Phe Trp Asp Tyr Asp Leu Val Asn Gly Gly
900 905 910

Ala Glu Pro Gln Pro Val Glu Asn Gly Leu Pro Leu Glu Gly Leu Leu
915 920 925

Gln Ser Ile Ile Asn Lys Lys Pro Val Leu Ile Pro Ile Ala Gly Glu
930 935 940

Gly Ala Ser Gln Met Glu Ile Glu Arg Glu Thr His Phe Asp Gly Thr
945 950 955 960

Asn Tyr Leu Ala Ile Arg Pro Gly Val Val Ile Gly Tyr Ser Arg Asn
965 970 975

Glu Lys Thr Asn Ala Ala Leu Glu Ala Ala Gly Ile Lys Val Leu Pro
980 985 990

Phe His Gly Asn Gln Leu Ser Leu Gly Met Gly Asn Ala Arg Cys Met
995 1000 1005

Ser Met Pro Leu Ser Arg Lys Asp Val Lys Trp
1010 1015

<210> 355
<211> 657
<212> PRT
<213> Homo sapiens

<400> 355
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Glu Gln Ala Pro Gly Thr Ala Pro
20 25 30

Cys Ser Arg Gly Ser Ser Trp Ser Ala Asp Leu Asp Lys Cys Met Asp
35 40 45

Cys Ala Ser Cys Arg Ala Arg Pro His Ser Asp Phe Cys Leu Gly Cys
50 55 60

Ala Ala Ala Pro Pro Ala Pro Phe Asp Ala His Lys Ser Glu Val Ala
65 70 75 80

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
85 90 95

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
100 105 110

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
115 120 125

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
130 135 140

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
145 150 155 160

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
165 170 175

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
180 185 190

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
195 200 205

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
210 215 220

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
225 230 235 240

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
245 250 255

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
260 265 270

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
275 280 285

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
290 295 300

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
305 310 315 320

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
325 330 335

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
340 345 350

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
355 360 365

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser

370 375 380

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
385 390 395 400

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
405 410 415

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
420 425 430

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
435 440 445

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
450 455 460

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
465 470 475 480

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
485 490 495

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
500 505 510

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
515 520 525

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
530 535 540

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
545 550 555 560

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
565 570 575

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
580 585 590

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
595 600 605

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
610 615 620

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
625 630 635 640

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
645 650 655

Leu

<210> 356
<211> 1106
<212> PRT
<213> Homo sapiens

<400> 356

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ala Arg Pro Cys Ile Pro Lys Ser
            20                  25                  30

Phe Gly Tyr Ser Ser Val Val Cys Val Cys Asn Ala Thr Tyr Cys Asp
        35                  40                  45

Ser Phe Asp Pro Pro Thr Phe Pro Ala Leu Gly Thr Phe Ser Arg Tyr
    50                  55                  60

Glu Ser Thr Arg Ser Gly Arg Arg Met Glu Leu Ser Met Gly Pro Ile
65                  70                  75                  80

Gln Ala Asn His Thr Gly Thr Gly Leu Leu Leu Thr Leu Gln Pro Glu
                85                  90                  95

Gln Lys Phe Gln Lys Val Lys Gly Phe Gly Gly Ala Met Thr Asp Ala
            100                 105                 110

Ala Ala Leu Asn Ile Leu Ala Leu Ser Pro Pro Ala Gln Asn Leu Leu
        115                 120                 125

Leu Lys Ser Tyr Phe Ser Glu Glu Gly Ile Gly Tyr Asn Ile Ile Arg
    130                 135                 140

Val Pro Met Ala Ser Cys Asp Phe Ser Ile Arg Thr Tyr Thr Tyr Ala
145                 150                 155                 160

Asp Thr Pro Asp Asp Phe Gln Leu His Asn Phe Ser Leu Pro Glu Glu
                165                 170                 175

Asp Thr Lys Leu Lys Ile Pro Leu Ile His Arg Ala Leu Gln Leu Ala
            180                 185                 190

Gln Arg Pro Val Ser Leu Leu Ala Ser Pro Trp Thr Ser Pro Thr Trp
        195                 200                 205

Leu Lys Thr Asn Gly Ala Val Asn Gly Lys Gly Ser Leu Lys Gly Gln
    210                 215                 220

Pro Gly Asp Ile Tyr His Gln Thr Trp Ala Arg Tyr Phe Val Lys Phe
225                 230                 235                 240

Leu Asp Ala Tyr Ala Glu His Lys Leu Gln Phe Trp Ala Val Thr Ala
                245                 250                 255

Glu Asn Glu Pro Ser Ala Gly Leu Leu Ser Gly Tyr Pro Phe Gln Cys
            260                 265                 270

Leu Gly Phe Thr Pro Glu His Gln Arg Asp Phe Ile Ala Arg Asp Leu
        275                 280                 285

Gly Pro Thr Leu Ala Asn Ser Thr His His Asn Val Arg Leu Leu Met
    290                 295                 300

Leu Asp Asp Gln Arg Leu Leu Leu Pro His Trp Ala Lys Val Val Leu
305                 310                 315                 320
```

Thr Asp Pro Glu Ala Ala Lys Tyr Val His Gly Ile Ala Val His Trp
325 330 335

Tyr Leu Asp Phe Leu Ala Pro Ala Lys Ala Thr Leu Gly Glu Thr His
340 345 350

Arg Leu Phe Pro Asn Thr Met Leu Phe Ala Ser Glu Ala Cys Val Gly
355 360 365

Ser Lys Phe Trp Glu Gln Ser Val Arg Leu Gly Ser Trp Asp Arg Gly
370 375 380

Met Gln Tyr Ser His Ser Ile Ile Thr Asn Leu Leu Tyr His Val Val
385 390 395 400

Gly Trp Thr Asp Trp Asn Leu Ala Leu Asn Pro Glu Gly Gly Pro Asn
405 410 415

Trp Val Arg Asn Phe Val Asp Ser Pro Ile Ile Val Asp Ile Thr Lys
420 425 430

Asp Thr Phe Tyr Lys Gln Pro Met Phe Tyr His Leu Gly His Phe Ser
435 440 445

Lys Phe Ile Pro Glu Gly Ser Gln Arg Val Gly Leu Val Ala Ser Gln
450 455 460

Lys Asn Asp Leu Asp Ala Val Ala Leu Met His Pro Asp Gly Ser Ala
465 470 475 480

Val Val Val Val Leu Asn Arg Ser Ser Lys Asp Val Pro Leu Thr Ile
485 490 495

Lys Asp Pro Ala Val Gly Phe Leu Glu Thr Ile Ser Pro Gly Tyr Ser
500 505 510

Ile His Thr Tyr Leu Trp Arg Arg Gln Asp Ala His Lys Ser Glu Val
515 520 525

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
530 535 540

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
545 550 555 560

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
565 570 575

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
580 585 590

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
595 600 605

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
610 615 620

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
625 630 635 640

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu

645 650 655

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
660 665 670

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
675 680 685

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
690 695 700

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
705 710 715 720

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
725 730 735

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
740 745 750

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
755 760 765

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
770 775 780

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
785 790 795 800

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
805 810 815

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
820 825 830

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
835 840 845

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
850 855 860

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
865 870 875 880

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
885 890 895

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
900 905 910

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
915 920 925

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
930 935 940

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
945 950 955 960

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
965 970 975

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
980 985 990

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
995 1000 1005

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
1010 1015 1020

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
1025 1030 1035 1040

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
1045 1050 1055

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
1060 1065 1070

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
1075 1080 1085

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
1090 1095 1100

Gly Leu
1105

<210> 357
<211> 1103
<212> PRT
<213> Homo sapiens

<400> 357
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ala Arg Pro Cys Ile Pro Lys Ser Phe Gly Tyr
20 25 30

Ser Ser Val Val Cys Val Cys Asn Ala Thr Tyr Cys Asp Ser Phe Asp
35 40 45

Pro Pro Thr Phe Pro Ala Leu Gly Thr Phe Ser Arg Tyr Glu Ser Thr
50 55 60

Arg Ser Gly Arg Arg Met Glu Leu Ser Met Gly Pro Ile Gln Ala Asn
65 70 75 80

His Thr Gly Thr Gly Leu Leu Leu Thr Leu Gln Pro Glu Gln Lys Phe
85 90 95

Gln Lys Val Lys Gly Phe Gly Gly Ala Met Thr Asp Ala Ala Ala Leu
100 105 110

Asn Ile Leu Ala Leu Ser Pro Pro Ala Gln Asn Leu Leu Leu Lys Ser
115 120 125

Tyr Phe Ser Glu Glu Gly Ile Gly Tyr Asn Ile Ile Arg Val Pro Met

130 135 140

Ala Ser Cys Asp Phe Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro
145 150 155 160

Asp Asp Phe Gln Leu His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys
165 170 175

Leu Lys Ile Pro Leu Ile His Arg Ala Leu Gln Leu Ala Gln Arg Pro
180 185 190

Val Ser Leu Leu Ala Ser Pro Trp Thr Ser Pro Thr Trp Leu Lys Thr
195 200 205

Asn Gly Ala Val Asn Gly Lys Gly Ser Leu Lys Gly Gln Pro Gly Asp
210 215 220

Ile Tyr His Gln Thr Trp Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala
225 230 235 240

Tyr Ala Glu His Lys Leu Gln Phe Trp Ala Val Thr Ala Glu Asn Glu
245 250 255

Pro Ser Ala Gly Leu Leu Ser Gly Tyr Pro Phe Gln Cys Leu Gly Phe
260 265 270

Thr Pro Glu His Gln Arg Asp Phe Ile Ala Arg Asp Leu Gly Pro Thr
275 280 285

Leu Ala Asn Ser Thr His His Asn Val Arg Leu Leu Met Leu Asp Asp
290 295 300

Gln Arg Leu Leu Leu Pro His Trp Ala Lys Val Val Leu Thr Asp Pro
305 310 315 320

Glu Ala Ala Lys Tyr Val His Gly Ile Ala Val His Trp Tyr Leu Asp
325 330 335

Phe Leu Ala Pro Ala Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe
340 345 350

Pro Asn Thr Met Leu Phe Ala Ser Glu Ala Cys Val Gly Ser Lys Phe
355 360 365

Trp Glu Gln Ser Val Arg Leu Gly Ser Trp Asp Arg Gly Met Gln Tyr
370 375 380

Ser His Ser Ile Ile Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr
385 390 395 400

Asp Trp Asn Leu Ala Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg
405 410 415

Asn Phe Val Asp Ser Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe
420 425 430

Tyr Lys Gln Pro Met Phe Tyr His Leu Gly His Phe Ser Lys Phe Ile
435 440 445

Pro Glu Gly Ser Gln Arg Val Gly Leu Val Ala Ser Gln Lys Asn Asp
450 455 460

Leu Asp Ala Val Ala Leu Met His Pro Asp Gly Ser Ala Val Val Val
465   470   475   480

Val Leu Asn Arg Ser Ser Lys Asp Val Pro Leu Thr Ile Lys Asp Pro
                485   490   495

Ala Val Gly Phe Leu Glu Thr Ile Ser Pro Gly Tyr Ser Ile His Thr
            500   505   510

Tyr Leu Trp Arg Arg Gln Asp Ala His Lys Ser Glu Val Ala His Arg
        515   520   525

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
    530   535   540

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
545   550   555   560

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
                565   570   575

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
            580   585   590

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
        595   600   605

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
    610   615   620

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
625   630   635   640

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
                645   650   655

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
            660   665   670

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
        675   680   685

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
    690   695   700

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
705   710   715   720

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
                725   730   735

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
            740   745   750

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
        755   760   765

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
    770   775   780

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
785 790 795 800

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
805 810 815

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
820 825 830

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
835 840 845

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
850 855 860

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
865 870 875 880

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
885 890 895

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
900 905 910

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
915 920 925

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
930 935 940

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
945 950 955 960

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
965 970 975

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
980 985 990

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
995 1000 1005

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
1010 1015 1020

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
1025 1030 1035 1040

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
1045 1050 1055

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
1060 1065 1070

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
1075 1080 1085

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
1090 1095 1100

<210> 358
<211> 1106
<212> PRT
<213> Homo sapiens

<400> 358
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20   25   30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35   40   45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50   55   60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65   70   75   80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85   90   95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100   105   110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115   120   125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130   135   140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145   150   155   160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165   170   175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180   185   190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195   200   205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210   215   220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225   230   235   240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245   250   255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260   265   270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275   280   285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ala Arg Pro Cys Ile Pro Lys Ser Phe Gly Tyr Ser Ser Val Val

610 615 620

Cys Val Cys Asn Ala Thr Tyr Cys Asp Ser Phe Asp Pro Pro Thr Phe
625 630 635 640

Pro Ala Leu Gly Thr Phe Ser Arg Tyr Glu Ser Thr Arg Ser Gly Arg
645 650 655

Arg Met Glu Leu Ser Met Gly Pro Ile Gln Ala Asn His Thr Gly Thr
660 665 670

Gly Leu Leu Leu Thr Leu Gln Pro Glu Gln Lys Phe Gln Lys Val Lys
675 680 685

Gly Phe Gly Gly Ala Met Thr Asp Ala Ala Ala Leu Asn Ile Leu Ala
690 695 700

Leu Ser Pro Pro Ala Gln Asn Leu Leu Leu Lys Ser Tyr Phe Ser Glu
705 710 715 720

Glu Gly Ile Gly Tyr Asn Ile Ile Arg Val Pro Met Ala Ser Cys Asp
725 730 735

Phe Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro Asp Asp Phe Gln
740 745 750

Leu His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys Leu Lys Ile Pro
755 760 765

Leu Ile His Arg Ala Leu Gln Leu Ala Gln Arg Pro Val Ser Leu Leu
770 775 780

Ala Ser Pro Trp Thr Ser Pro Thr Trp Leu Lys Thr Asn Gly Ala Val
785 790 795 800

Asn Gly Lys Gly Ser Leu Lys Gly Gln Pro Gly Asp Ile Tyr His Gln
805 810 815

Thr Trp Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala Tyr Ala Glu His
820 825 830

Lys Leu Gln Phe Trp Ala Val Thr Ala Glu Asn Glu Pro Ser Ala Gly
835 840 845

Leu Leu Ser Gly Tyr Pro Phe Gln Cys Leu Gly Phe Thr Pro Glu His
850 855 860

Gln Arg Asp Phe Ile Ala Arg Asp Leu Gly Pro Thr Leu Ala Asn Ser
865 870 875 880

Thr His His Asn Val Arg Leu Leu Met Leu Asp Asp Gln Arg Leu Leu
885 890 895

Leu Pro His Trp Ala Lys Val Val Leu Thr Asp Pro Glu Ala Ala Lys
900 905 910

Tyr Val His Gly Ile Ala Val His Trp Tyr Leu Asp Phe Leu Ala Pro
915 920 925

Ala Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe Pro Asn Thr Met
930 935 940

Leu Phe Ala Ser Glu Ala Cys Val Gly Ser Lys Phe Trp Glu Gln Ser
945 950 955 960

Val Arg Leu Gly Ser Trp Asp Arg Gly Met Gln Tyr Ser His Ser Ile
965 970 975

Ile Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr Asp Trp Asn Leu
980 985 990

Ala Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg Asn Phe Val Asp
995 1000 1005

Ser Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe Tyr Lys Gln Pro
1010 1015 1020

Met Phe Tyr His Leu Gly His Phe Ser Lys Phe Ile Pro Glu Gly Ser
1025 1030 1035 1040

Gln Arg Val Gly Leu Val Ala Ser Gln Lys Asn Asp Leu Asp Ala Val
1045 1050 1055

Ala Leu Met His Pro Asp Gly Ser Ala Val Val Val Val Leu Asn Arg
1060 1065 1070

Ser Ser Lys Asp Val Pro Leu Thr Ile Lys Asp Pro Ala Val Gly Phe
1075 1080 1085

Leu Glu Thr Ile Ser Pro Gly Tyr Ser Ile His Thr Tyr Leu Trp Arg
1090 1095 1100

Arg Gln
1105

<210> 359
<211> 1106
<212> PRT
<213> Homo sapiens

<400> 359
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala

```
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430
```

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ala Arg Pro Cys Ile Pro Lys Ser Phe Gly Tyr Ser Ser Val Val
610 615 620

Cys Val Cys Asn Ala Thr Tyr Cys Asp Ser Phe Asp Pro Pro Thr Phe
625 630 635 640

Pro Ala Leu Gly Thr Phe Ser Arg Tyr Glu Ser Thr Arg Ser Gly Arg
645 650 655

Arg Met Glu Leu Ser Met Gly Pro Ile Gln Ala Asn His Thr Gly Thr
660 665 670

Gly Leu Leu Leu Thr Leu Gln Pro Glu Gln Lys Phe Gln Lys Val Lys
675 680 685

Gly Phe Gly Gly Ala Met Thr Asp Ala Ala Ala Leu Asn Ile Leu Ala
690 695 700

Leu Ser Pro Pro Ala Gln Asn Leu Leu Leu Lys Ser Tyr Phe Ser Glu
705 710 715 720

Glu Gly Ile Gly Tyr Asn Ile Ile Arg Val Pro Met Ala Ser Cys Asp
725 730 735

Phe Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro Asp Asp Phe Gln
740 745 750

Leu His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys Leu Lys Ile Pro
755 760 765

Leu Ile His Arg Ala Leu Gln Leu Ala Gln Arg Pro Val Ser Leu Leu
770 775 780

Ala Ser Pro Trp Thr Ser Pro Thr Trp Leu Lys Thr Asn Gly Ala Val
785 790 795 800

Asn Gly Lys Gly Ser Leu Lys Gly Gln Pro Gly Asp Ile Tyr His Gln
805 810 815

Thr Trp Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala Tyr Ala Glu His
820 825 830

Lys Leu Gln Phe Trp Ala Val Thr Ala Glu Asn Glu Pro Ser Ala Gly
835 840 845

Leu Leu Ser Gly Tyr Pro Phe Gln Cys Leu Gly Phe Thr Pro Glu His
850 855 860

Gln Arg Asp Phe Ile Ala Arg Asp Leu Gly Pro Thr Leu Ala Asn Ser
865 870 875 880

Thr His His Asn Val Arg Leu Leu Met Leu Asp Asp Gln Arg Leu Leu
885 890 895

Leu Pro His Trp Ala Lys Val Val Leu Thr Asp Pro Glu Ala Ala Lys
900 905 910

Tyr Val His Gly Ile Ala Val His Trp Tyr Leu Asp Phe Leu Ala Pro
915 920 925

Ala Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe Pro Asn Thr Met
930 935 940

Leu Phe Ala Ser Glu Ala Cys Val Gly Ser Lys Phe Trp Glu Gln Ser
945 950 955 960

Val Arg Leu Gly Ser Trp Asp Arg Gly Met Gln Tyr Ser His Ser Ile
965 970 975

Ile Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr Asp Trp Asn Leu
980 985 990

Ala Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg Asn Phe Val Asp
995 1000 1005

Ser Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe Tyr Lys Gln Pro
1010 1015 1020

Met Phe Tyr His Leu Gly His Phe Ser Lys Phe Ile Pro Glu Gly Ser
1025 1030 1035 1040

Gln Arg Val Gly Leu Val Ala Ser Gln Lys Asn Asp Leu Asp Ala Val
1045 1050 1055

Ala Leu Met His Pro Asp Gly Ser Ala Val Val Val Val Leu Asn Arg
1060 1065 1070

Ser Ser Lys Asp Val Pro Leu Thr Ile Lys Asp Pro Ala Val Gly Phe

1075 1080 1085

Leu Glu Thr Ile Ser Pro Gly Tyr Ser Ile His Thr Tyr Leu Trp Arg
1090 1095 1100

Arg Gln
1105

<210> 360
<211> 661
<212> PRT
<213> Homo sapiens

<400> 360
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Tyr Arg Gln Ser Met Asn Asn Phe
20 25 30

Gln Gly Leu Arg Ser Phe Gly Cys Arg Phe Gly Thr Cys Thr Val Gln
35 40 45

Lys Leu Ala His Gln Ile Tyr Gln Phe Thr Asp Lys Asp Lys Asp Asn
50 55 60

Val Ala Pro Arg Ser Lys Ile Ser Pro Gln Gly Tyr Asp Ala His Lys
65 70 75 80

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
85 90 95

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
100 105 110

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
115 120 125

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
130 135 140

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
145 150 155 160

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
165 170 175

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
180 185 190

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
195 200 205

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
210 215 220

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
225 230 235 240

```
Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
                245                 250                 255

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
            260                 265                 270

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
        275                 280                 285

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
    290                 295                 300

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
305                 310                 315                 320

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
                325                 330                 335

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
            340                 345                 350

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
        355                 360                 365

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
    370                 375                 380

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
385                 390                 395                 400

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
                405                 410                 415

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
            420                 425                 430

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
        435                 440                 445

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
    450                 455                 460

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
465                 470                 475                 480

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
                485                 490                 495

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
            500                 505                 510

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
        515                 520                 525

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
    530                 535                 540

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
545                 550                 555                 560

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
```

565 570 575

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
580 585 590

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
595 600 605

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
610 615 620

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
625 630 635 640

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
645 650 655

Ala Ala Leu Gly Leu
660

<210> 361
<211> 658
<212> PRT
<213> Homo sapiens

<400> 361
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu
20 25 30

Arg Ser Phe Gly Cys Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala
35 40 45

His Gln Ile Tyr Gln Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro
50 55 60

Arg Ser Lys Ile Ser Pro Gln Gly Tyr Asp Ala His Lys Ser Glu Val
65 70 75 80

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
85 90 95

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
100 105 110

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
115 120 125

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
130 135 140

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
145 150 155 160

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
165 170 175

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
180 185 190

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
195 200 205

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
210 215 220

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
225 230 235 240

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
245 250 255

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
260 265 270

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
275 280 285

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
290 295 300

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
305 310 315 320

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
325 330 335

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
340 345 350

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
355 360 365

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
370 375 380

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
385 390 395 400

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
405 410 415

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
420 425 430

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
435 440 445

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
450 455 460

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
465 470 475 480

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
485 490 495

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys

500 505 510

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
515 520 525

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
530 535 540

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
545 550 555 560

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
565 570 575

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
580 585 590

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
595 600 605

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
610 615 620

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
625 630 635 640

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
645 650 655

Gly Leu

<210> 362
<211> 661
<212> PRT
<213> Homo sapiens

<400> 362
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

```
His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445
```

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly
610 615 620

Cys Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr
625 630 635 640

Gln Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile
645 650 655

Ser Pro Gln Gly Tyr
660

<210> 363
<211> 661
<212> PRT
<213> Homo sapiens

<400> 363
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

```
Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly
    610                 615                 620

Cys Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr
625                 630                 635                 640

Gln Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile
                645                 650                 655

Ser Pro Gln Gly Tyr
            660


<210> 364
<211> 735
<212> PRT
<213> Homo sapiens
```

<400> 364
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Glu Pro Leu Glu Lys Val Ala Ser Val Gly Asn Ser Arg Pro Thr
610 615 620

Gly Gln Gln Leu Glu Ser Leu Gly Leu Leu Ala Pro Gly Glu Gln Ser
625 630 635 640

Leu Pro Cys Thr Glu Arg Lys Pro Ala Ala Thr Ala Arg Leu Ser Arg

645 650 655

Arg Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Pro Gln
660 665 670

Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln
675 680 685

Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp
690 695 700

Asn Ser Phe Gly Leu Arg Phe Gly Lys Arg Glu Ala Ala Pro Gly Asn
705 710 715 720

His Gly Arg Ser Ala Gly Arg Gly Trp Gly Ala Gly Ala Gly Gln
725 730 735

<210> 365
<211> 735
<212> PRT
<213> Homo sapiens

<400> 365
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

```
Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
```

515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Glu Pro Leu Glu Lys Val Ala Ser Val Gly Asn Ser Arg Pro Thr
610 615 620

Gly Gln Gln Leu Glu Ser Leu Gly Leu Leu Ala Pro Gly Glu Gln Ser
625 630 635 640

Leu Pro Cys Thr Glu Arg Lys Pro Ala Ala Thr Ala Arg Leu Ser Arg
645 650 655

Arg Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Pro Gln
660 665 670

Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln
675 680 685

Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp
690 695 700

Asn Ser Phe Gly Leu Arg Phe Gly Lys Arg Glu Ala Ala Pro Gly Asn
705 710 715 720

His Gly Arg Ser Ala Gly Arg Gly Trp Gly Ala Gly Ala Gly Gln
725 730 735

<210> 366
<211> 809
<212> PRT
<213> Homo sapiens

<400> 366
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Lys Asn Leu Glu Pro Val Ser Trp
20 25 30

Ser Ser Leu Asn Pro Lys Phe Leu Ser Gly Lys Gly Leu Val Ile Tyr
35 40 45

Pro Lys Ile Gly Asp Lys Leu Asp Ile Ile Cys Pro Arg Ala Glu Ala
50 55 60

Gly Arg Pro Tyr Glu Tyr Tyr Lys Leu Tyr Leu Val Arg Pro Glu Gln
65 70 75 80

Ala Ala Ala Cys Ser Thr Val Leu Asp Pro Asn Val Leu Val Thr Cys
85 90 95

Asn Arg Pro Glu Gln Glu Ile Arg Phe Thr Ile Lys Phe Gln Glu Phe
100 105 110

Ser Pro Asn Tyr Met Gly Leu Glu Phe Lys Lys His His Asp Tyr Tyr
115 120 125

Ile Thr Ser Thr Ser Asn Gly Ser Leu Glu Gly Leu Glu Asn Arg Glu
130 135 140

Gly Gly Val Cys Arg Thr Arg Thr Met Lys Ile Ile Met Lys Val Gly
145 150 155 160

Gln Asp Pro Asn Ala Val Thr Pro Glu Gln Leu Thr Thr Ser Arg Pro
165 170 175

Ser Lys Glu Ala Asp Asn Thr Val Lys Met Ala Thr Gln Ala Pro Gly
180 185 190

Ser Arg Gly Ser Leu Gly Asp Ser Asp Gly Lys His Glu Thr Val Asn
195 200 205

Gln Glu Glu Lys Ser Gly Pro Gly Ala Ser Gly Gly Ser Ser Gly Asp
210 215 220

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
225 230 235 240

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
245 250 255

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
260 265 270

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
275 280 285

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
290 295 300

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
305 310 315 320

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
325 330 335

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
340 345 350

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
355 360 365

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
370 375 380

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala

385 390 395 400

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
405 410 415

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
420 425 430

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
435 440 445

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
450 455 460

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
465 470 475 480

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
485 490 495

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
500 505 510

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
515 520 525

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
530 535 540

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
545 550 555 560

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
565 570 575

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
580 585 590

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
595 600 605

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
610 615 620

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
625 630 635 640

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
645 650 655

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
660 665 670

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
675 680 685

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
690 695 700

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
705 710 715 720

```
Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
                725                 730                 735

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
            740                 745                 750

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
        755                 760                 765

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
    770                 775                 780

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
785                 790                 795                 800

Ala Ala Ser Gln Ala Ala Leu Gly Leu
                805
```

<210> 367
<211> 814
<212> PRT
<213> Homo sapiens

<400> 367

```
Met Ala Arg Pro Gly Gln Arg Trp Leu Gly Lys Trp Leu Val Ala Met
1               5                   10                  15

Val Val Trp Ala Leu Cys Arg Leu Ala Thr Pro Leu Ala Lys Asn Leu
            20                  25                  30

Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe Leu Ser Gly Lys
        35                  40                  45

Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu Asp Ile Ile Cys
    50                  55                  60

Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr Lys Leu Tyr Leu
65                  70                  75                  80

Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val Leu Asp Pro Asn
                85                  90                  95

Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile Arg Phe Thr Ile
            100                 105                 110

Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu Glu Phe Lys Lys
        115                 120                 125

His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly Ser Leu Glu Gly
    130                 135                 140

Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg Thr Met Lys Ile
145                 150                 155                 160

Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr Pro Glu Gln Leu
                165                 170                 175

Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr Val Lys Met Ala
```

180 185 190

Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp Ser Asp Gly Lys
195 200 205

His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro Gly Ala Ser Gly
210 215 220

Gly Ser Ser Gly Asp Asp Ala His Lys Ser Glu Val Ala His Arg Phe
225 230 235 240

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
245 250 255

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
260 265 270

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
275 280 285

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
290 295 300

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
305 310 315 320

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
325 330 335

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
340 345 350

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
355 360 365

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
370 375 380

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
385 390 395 400

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
405 410 415

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
420 425 430

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
435 440 445

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
450 455 460

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
465 470 475 480

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
485 490 495

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
500 505 510

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
        515   520   525

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
    530   535   540

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
545   550   555   560

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
                565   570   575

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
            580   585   590

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
        595   600   605

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
    610   615   620

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
625   630   635   640

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
                645   650   655

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
            660   665   670

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
        675   680   685

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
    690   695   700

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
705   710   715   720

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
                725   730   735

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
            740   745   750

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
        755   760   765

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
    770   775   780

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
785   790   795   800

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                805   810

<210> 368

<211> 660
<212> PRT
<213> Homo sapiens

<400> 368
Met Ala Arg Gly Ser Leu Arg Arg Leu Leu Arg Leu Leu Val Leu Gly
1   5   10   15

Leu Trp Leu Ala Leu Leu Arg Ser Val Ala Gly Glu Gln Ala Pro Gly
            20   25   30

Thr Ala Pro Cys Ser Arg Gly Ser Ser Trp Ser Ala Asp Leu Asp Lys
        35   40   45

Cys Met Asp Cys Ala Ser Cys Arg Ala Arg Pro His Ser Asp Phe Cys
    50   55   60

Leu Gly Cys Ala Ala Ala Pro Pro Ala Pro Phe Asp Ala His Lys Ser
65   70   75   80

Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala
                85   90   95

Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu
            100   105   110

Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys
        115   120   125

Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu
    130   135   140

Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly
145   150   155   160

Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys
                165   170   175

Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg
            180   185   190

Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr
        195   200   205

Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe
    210   215   220

Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe
225   230   235   240

Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys
                245   250   255

Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg
            260   265   270

Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
        275   280   285

Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala
    290   295   300

Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys
305 310 315 320

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala
325 330 335

Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu
340 345 350

Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val
355 360 365

Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe
370 375 380

Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
385 390 395 400

Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr
405 410 415

Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu
420 425 430

Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val
435 440 445

Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys
450 455 460

Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn
465 470 475 480

Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro
485 490 495

Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys
500 505 510

Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu
515 520 525

Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val
530 535 540

Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg
545 550 555 560

Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu
565 570 575

Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser
580 585 590

Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val
595 600 605

Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp
610 615 620

Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu
625 630 635 640

Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala
645 650 655

Ala Leu Gly Leu
660

<210> 369
<211> 832
<212> PRT
<213> Homo sapiens

<400> 369
Met Leu Arg Arg Arg Gly Ser Pro Gly Met Gly Val His Val Gly Ala
1 5 10 15

Ala Leu Gly Ala Leu Trp Phe Cys Leu Thr Gly Ala Leu Glu Val Gln
20 25 30

Val Pro Glu Asp Pro Val Val Ala Leu Val Gly Thr Asp Ala Thr Leu
35 40 45

Cys Cys Ser Phe Ser Pro Glu Pro Gly Phe Ser Leu Ala Gln Leu Asn
50 55 60

Leu Ile Trp Gln Leu Thr Asp Thr Lys Gln Leu Val His Ser Phe Ala
65 70 75 80

Glu Gly Gln Asp Gln Gly Ser Ala Tyr Ala Asn Arg Thr Ala Leu Phe
85 90 95

Leu Asp Leu Leu Ala Gln Gly Asn Ala Ser Leu Arg Leu Gln Arg Val
100 105 110

Arg Val Ala Asp Glu Gly Ser Phe Thr Cys Phe Val Ser Ile Arg Asp
115 120 125

Phe Gly Ser Ala Ala Val Ser Leu Gln Val Ala Ala Pro Tyr Ser Lys
130 135 140

Pro Ser Met Thr Leu Glu Pro Asn Lys Asp Leu Arg Pro Gly Asp Thr
145 150 155 160

Val Thr Ile Thr Cys Ser Ser Tyr Arg Gly Tyr Pro Glu Ala Glu Val
165 170 175

Phe Trp Gln Asp Gly Gln Gly Val Pro Leu Thr Gly Asn Val Thr Thr
180 185 190

Ser Gln Met Ala Asn Glu Gln Gly Leu Phe Asp Val His Ser Val Leu
195 200 205

Arg Val Val Leu Gly Ala Asn Gly Thr Tyr Ser Cys Leu Val Arg Asn
210 215 220

Pro Val Leu Gln Gln Asp Ala His Gly Ser Val Thr Ile Thr Gly Gln
225 230 235 240

Pro Met Thr Phe Pro Pro Glu Asp Ala His Lys Ser Glu Val Ala His
245 250 255

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
260 265 270

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
275 280 285

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
290 295 300

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
305 310 315 320

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
325 330 335

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
340 345 350

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
355 360 365

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
370 375 380

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
385 390 395 400

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
405 410 415

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
420 425 430

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
435 440 445

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
450 455 460

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
465 470 475 480

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
485 490 495

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
500 505 510

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
515 520 525

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
530 535 540

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
545 550 555 560

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
565 570 575

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
580 585 590

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
595 600 605

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
610 615 620

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
625 630 635 640

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
645 650 655

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
660 665 670

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
675 680 685

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
690 695 700

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
705 710 715 720

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
725 730 735

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
740 745 750

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
755 760 765

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
770 775 780

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
785 790 795 800

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
805 810 815

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
820 825 830

<210> 370
<211> 809
<212> PRT
<213> Homo sapiens

<400> 370
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

```
Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335
```

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Lys Asn Leu Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe
610 615 620

Leu Ser Gly Lys Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu
625 630 635 640

Asp Ile Ile Cys Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr
645 650 655

Lys Leu Tyr Leu Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val

660 665 670

Leu Asp Pro Asn Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile
675 680 685

Arg Phe Thr Ile Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu
690 695 700

Glu Phe Lys Lys His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly
705 710 715 720

Ser Leu Glu Gly Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg
725 730 735

Thr Met Lys Ile Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr
740 745 750

Pro Glu Gln Leu Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr
755 760 765

Val Lys Met Ala Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp
770 775 780

Ser Asp Gly Lys His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro
785 790 795 800

Gly Ala Ser Gly Gly Ser Ser Gly Asp
805

<210> 371
<211> 809
<212> PRT
<213> Homo sapiens

<400> 371
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

```
His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
```

450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Lys Asn Leu Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe
610 615 620

Leu Ser Gly Lys Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu
625 630 635 640

Asp Ile Ile Cys Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr
645 650 655

Lys Leu Tyr Leu Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val
660 665 670

Leu Asp Pro Asn Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile
675 680 685

Arg Phe Thr Ile Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu
690 695 700

Glu Phe Lys Lys His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly
705 710 715 720

Ser Leu Glu Gly Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg
725 730 735

Thr Met Lys Ile Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr
740 745 750

Pro Glu Gln Leu Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr
755 760 765

Val Lys Met Ala Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp
770 775 780

Ser Asp Gly Lys His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro
785 790 795 800

Gly Ala Ser Gly Gly Ser Ser Gly Asp
805

<210> 372
<211> 925
<212> PRT
<213> Homo sapiens

<400> 372
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Met Pro Val Phe Ser Leu Gln Asn Asp Glu Val
20 25 30

Glu Phe Val Arg Thr Gly Tyr Gly Lys Asp Ile Val Lys Val Leu His
35 40 45

Ile Gln Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser
50 55 60

Val Gln Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn
65 70 75 80

Ser Asp Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu
85 90 95

Ala Lys Phe Lys Glu Asn Glu Pro Ala Asn Ile Asp Gly Ala Met Glu
100 105 110

Lys Ala Phe Cys Phe Phe Leu Gln Ile Lys Ser Ile Glu Ala Phe Gly
115 120 125

Val Asn Ile Cys Glu His Phe Leu Ser Ser Phe Asn His Val Ile Arg
130 135 140

Ala Gln Val Tyr Val Glu Glu Ile Pro Trp Lys His Leu Glu Lys Asn
145 150 155 160

Gly Val Lys His Val His Ala Phe Ile His Thr Pro Thr Gly Thr His
165 170 175

Phe Gly Glu Val Glu Gln Leu Arg Ser Gly Pro Gln Val Ile His Ser
180 185 190

Gly Ile Lys Asp Leu Lys Leu Leu Lys Thr Thr Gln Ser Gly Phe Glu
195 200 205

Gly Phe Ile Lys Asp Gln Phe Thr Thr Leu Pro Glu Val Phe Lys Cys
210 215 220

Met Met Arg Thr Leu Pro Gln Ser Ser Phe Pro Leu Phe Gln Val Leu
225 230 235 240

Ser Met Gly Ser Ser Leu Met Asp Thr Ile Arg Asp Leu Val Met Glu

245 250 255

Lys Ser Ala Gly Pro Tyr Asp Lys Asp Glu Tyr Ser Pro Ser Val Gln
260 265 270

Lys Thr Leu Cys Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro Ala
275 280 285

Ile Glu Asp Met Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile
290 295 300

Asp Met Ser Lys Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro
305 310 315 320

Leu Asp Asn Pro Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu
325 330 335

Ser Ser Arg Leu Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
340 345 350

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
355 360 365

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
370 375 380

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
385 390 395 400

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
405 410 415

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
420 425 430

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
435 440 445

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
450 455 460

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
465 470 475 480

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
485 490 495

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
500 505 510

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
515 520 525

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
530 535 540

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
545 550 555 560

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
565 570 575

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
580 585 590

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
595 600 605

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
610 615 620

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
625 630 635 640

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
645 650 655

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
660 665 670

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
675 680 685

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
690 695 700

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
705 710 715 720

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
725 730 735

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
740 745 750

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
755 760 765

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
770 775 780

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
785 790 795 800

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
805 810 815

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
820 825 830

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
835 840 845

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
850 855 860

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
865 870 875 880

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
885 890 895

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
900 905 910

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
915 920 925

<210> 373
<211> 928
<212> PRT
<213> Homo sapiens

<400> 373
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Pro Val Phe Ser Leu Gln Asn Asp Glu Val Glu Phe Val Arg
610 615 620

Thr Gly Tyr Gly Lys Asp Ile Val Lys Val Leu His Ile Gln Arg Asp
625 630 635 640

Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln Leu Thr
645 650 655

Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp Ile Ile
660 665 670

Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys Phe Lys
675 680 685

Glu Asn Glu Pro Ala Asn Ile Asp Gly Ala Met Glu Lys Ala Phe Cys
690 695 700

Phe Phe Leu Gln Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys
705 710 715 720

Glu His Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr
725 730 735

Val Glu Glu Ile Pro Trp Lys His Leu Glu Lys Asn Gly Val Lys His
740 745 750

Val His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Gly Glu Val
755 760 765

Glu Gln Leu Arg Ser Gly Pro Gln Val Ile His Ser Gly Ile Lys Asp
770 775 780

Leu Lys Leu Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys
785 790 795 800

Asp Gln Phe Thr Thr Leu Pro Glu Val Phe Lys Cys Met Met Arg Thr
805 810 815

Leu Pro Gln Ser Ser Phe Pro Leu Phe Gln Val Leu Ser Met Gly Ser
820 825 830

Ser Leu Met Asp Thr Ile Arg Asp Leu Val Met Glu Lys Ser Ala Gly
835 840 845

Pro Tyr Asp Lys Asp Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Cys
850 855 860

Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro Ala Ile Glu Asp Met
865 870 875 880

Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys
885 890 895

Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro

900 905 910

Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
915 920 925

<210> 374
<211> 1000
<212> PRT
<213> Homo sapiens

<400> 374
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Met Glu Lys Phe Ile Trp Tyr Leu Val His Leu
20 25 30

Tyr Thr Glu Met Thr Lys Ser Ser Pro Ser Cys Arg Leu Val Ala Ser
35 40 45

Cys Gln Thr Val Ala Lys Glu Leu Gly Glu Asn Ser Leu Gly Tyr Gly
50 55 60

Pro Gly His Tyr Leu Leu Phe Gly Cys Arg Asp Ala Phe Gly Cys Pro
65 70 75 80

Met Pro Gly Leu Phe His Leu Leu Gln Asp Gln Met Ile Gly Ser Leu
85 90 95

His Thr Asp Ser Leu Pro Asn Asp Glu Val Glu Phe Val Arg Thr Gly
100 105 110

Tyr Gly Lys Glu Met Val Lys Val Leu His Ile Gln Arg Asp Gly Lys
115 120 125

Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln Leu Thr Leu Ser
130 135 140

Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp Ile Ile Pro Thr
145 150 155 160

Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys Phe Lys Glu Asn
165 170 175

Asp Pro Ala Asn Ile Asp Gly Ala Met Glu Lys Ala Phe Cys Phe Phe
180 185 190

Leu Gln Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu His
195 200 205

Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr Met Glu
210 215 220

Glu Ile Pro Trp Lys His Leu Gly Lys Asn Gly Val Lys His Val His
225 230 235 240

Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu Gln
245 250 255

Leu Arg Ser Gly Pro Gln Val Ile His Ser Gly Ile Lys Asp Leu Lys
260 265 270

Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp Gln
275 280 285

Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln Val
290 295 300

Tyr Cys Lys Trp Arg Tyr His Gln Cys Arg Asp Val Asp Phe Lys Ala
305 310 315 320

Thr Trp Asp Thr Ile Arg Asp Leu Val Met Glu Lys Ser Ala Gly Pro
325 330 335

Tyr Asp Lys Gly Glu Tyr Leu Thr Ser Val Gln Lys Thr Leu Cys Asp
340 345 350

Ile Gln Val Leu Ser Leu Ser Arg Val Pro Ala Ile Glu Asp Met Glu
355 360 365

Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met
370 375 380

Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr
385 390 395 400

Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu Asp
405 410 415

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
420 425 430

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
435 440 445

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
450 455 460

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
465 470 475 480

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
485 490 495

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
500 505 510

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
515 520 525

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
530 535 540

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
545 550 555 560

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
565 570 575

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys

580 585 590

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
595 600 605

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
610 615 620

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
625 630 635 640

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
645 650 655

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
660 665 670

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
675 680 685

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
690 695 700

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
705 710 715 720

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
725 730 735

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
740 745 750

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
755 760 765

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
770 775 780

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
785 790 795 800

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
805 810 815

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
820 825 830

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
835 840 845

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
850 855 860

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
865 870 875 880

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
885 890 895

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
900 905 910

```
Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
        915                 920                 925

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
    930                 935                 940

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
945                 950                 955                 960

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
                965                 970                 975

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
            980                 985                 990

Ala Ser Gln Ala Ala Leu Gly Leu
        995                 1000


&lt;210&gt; 375
&lt;211&gt; 1003
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 375
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
```

180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Glu Lys Phe Ile Trp Tyr Leu Val His Leu Tyr Thr Glu Met
610 615 620

Thr Lys Ser Ser Pro Ser Cys Arg Leu Val Ala Ser Cys Gln Thr Val
625 630 635 640

Ala Lys Glu Leu Gly Glu Asn Ser Leu Gly Tyr Gly Pro Gly His Tyr
645 650 655

Leu Leu Phe Gly Cys Arg Asp Ala Phe Gly Cys Pro Met Pro Gly Leu
660 665 670

Phe His Leu Leu Gln Asp Gln Met Ile Gly Ser Leu His Thr Asp Ser
675 680 685

Leu Pro Asn Asp Glu Val Glu Phe Val Arg Thr Gly Tyr Gly Lys Glu
690 695 700

Met Val Lys Val Leu His Ile Gln Arg Asp Gly Lys Tyr His Ser Ile
705 710 715 720

Lys Glu Val Ala Thr Ser Val Gln Leu Thr Leu Ser Ser Lys Lys Asp
725 730 735

Tyr Leu His Gly Asp Asn Ser Asp Ile Ile Pro Thr Asp Thr Ile Lys
740 745 750

Asn Thr Val His Val Leu Ala Lys Phe Lys Glu Asn Asp Pro Ala Asn
755 760 765

Ile Asp Gly Ala Met Glu Lys Ala Phe Cys Phe Phe Leu Gln Ile Lys
770 775 780

Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu His Phe Leu Ser Ser
785 790 795 800

Phe Asn His Val Ile Arg Ala Gln Val Tyr Met Glu Glu Ile Pro Trp
805 810 815

Lys His Leu Gly Lys Asn Gly Val Lys His Val His Ala Phe Ile His
820 825 830

```
Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu Gln Leu Arg Ser Gly
        835                 840                 845

Pro Gln Val Ile His Ser Gly Ile Lys Asp Leu Lys Val Leu Lys Thr
    850                 855                 860

Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp Gln Phe Thr Thr Leu
865                 870                 875                 880

Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln Val Tyr Cys Lys Trp
                885                 890                 895

Arg Tyr His Gln Cys Arg Asp Val Asp Phe Lys Ala Thr Trp Asp Thr
            900                 905                 910

Ile Arg Asp Leu Val Met Glu Lys Ser Ala Gly Pro Tyr Asp Lys Gly
        915                 920                 925

Glu Tyr Leu Thr Ser Val Gln Lys Thr Leu Cys Asp Ile Gln Val Leu
    930                 935                 940

Ser Leu Ser Arg Val Pro Ala Ile Glu Asp Met Glu Ile Ser Leu Pro
945                 950                 955                 960

Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met Gly Leu Ile Asn
                965                 970                 975

Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr Gly Lys Ile Thr
            980                 985                 990

Gly Thr Val Lys Arg Lys Leu Ser  Ser Arg Leu
        995                 1000


<210> 376
<211> 910
<212> PRT
<213> Homo sapiens

<400> 376
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
  1               5                  10                  15

Pro Met Val Trp Ala Met Ala Asp Tyr His Asn Asn Tyr Lys Lys Asn
            20                  25                  30

Asp Glu Leu Glu Phe Val Arg Thr Gly Tyr Gly Lys Asp Met Val Lys
        35                  40                  45

Val Leu His Ile Gln Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val
    50                  55                  60

Ala Thr Ser Val Gln Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His
65                  70                  75                  80

Gly Asp Asn Ser Asp Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val
                85                  90                  95

His Val Leu Ala Lys Phe Lys Gly Ile Lys Ser Ile Glu Ala Phe Gly
            100                 105                 110
```

Val Asn Ile Cys Glu Tyr Phe Leu Ser Ser Phe Asn His Val Ile Arg
115 120 125

Ala Gln Val Tyr Val Glu Glu Ile Pro Trp Lys Arg Leu Glu Lys Asn
130 135 140

Gly Val Lys His Val His Ala Phe Ile His Thr Pro Thr Gly Thr His
145 150 155 160

Phe Cys Glu Val Glu Gln Leu Arg Ser Gly Pro Pro Val Ile His Ser
165 170 175

Gly Ile Lys Asp Leu Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu
180 185 190

Gly Phe Ile Lys Asp Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg
195 200 205

Cys Phe Ala Thr Gln Val Tyr Cys Lys Trp Arg Tyr His Gln Cys Arg
210 215 220

Asp Val Asp Phe Glu Ala Thr Trp Gly Thr Ile Arg Asp Leu Val Leu
225 230 235 240

Glu Lys Phe Ala Gly Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val
245 250 255

Gln Lys Thr Leu Tyr Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro
260 265 270

Glu Ile Glu Asp Met Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn
275 280 285

Ile Asp Met Ser Lys Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu
290 295 300

Pro Leu Asp Asn Pro Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys
305 310 315 320

Leu Ser Ser Arg Leu Asp Ala His Lys Ser Glu Val Ala His Arg Phe
325 330 335

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
340 345 350

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
355 360 365

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
370 375 380

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
385 390 395 400

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
405 410 415

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
420 425 430

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met

435 440 445

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
450 455 460

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
465 470 475 480

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
485 490 495

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
500 505 510

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
515 520 525

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
530 535 540

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
545 550 555 560

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
565 570 575

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
580 585 590

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
595 600 605

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
610 615 620

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
625 630 635 640

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
645 650 655

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
660 665 670

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
675 680 685

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
690 695 700

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
705 710 715 720

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
725 730 735

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
740 745 750

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
755 760 765

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
    770   775   780

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
785   790   795   800

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
                805   810   815

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
            820   825   830

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
        835   840   845

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
    850   855   860

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
865   870   875   880

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
                885   890   895

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            900   905   910

<210> 377
<211> 913
<212> PRT
<213> Homo sapiens

<400> 377
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1   5   10   15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20   25   30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35   40   45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50   55   60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65   70   75   80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85   90   95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100   105   110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115   120   125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130   135   140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Ala Asp Tyr His Asn Asn Tyr Lys Lys Asn Asp Glu Leu Glu
610 615 620

Phe Val Arg Thr Gly Tyr Gly Lys Asp Met Val Lys Val Leu His Ile
625 630 635 640

Gln Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val
645 650 655

Gln Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser
660 665 670

Asp Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala
675 680 685

Lys Phe Lys Gly Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys
690 695 700

Glu Tyr Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr
705 710 715 720

Val Glu Glu Ile Pro Trp Lys Arg Leu Glu Lys Asn Gly Val Lys His
725 730 735

Val His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Glu Val
740 745 750

Glu Gln Leu Arg Ser Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp
755 760 765

Leu Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys
770 775 780

Asp Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr

785 790 795 800

Gln Val Tyr Cys Lys Trp Arg Tyr His Gln Cys Arg Asp Val Asp Phe
805 810 815

Glu Ala Thr Trp Gly Thr Ile Arg Asp Leu Val Leu Glu Lys Phe Ala
820 825 830

Gly Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu
835 840 845

Tyr Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro Glu Ile Glu Asp
850 855 860

Met Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser
865 870 875 880

Lys Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn
885 890 895

Pro Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg
900 905 910

Leu

<210> 378
<211> 1003
<212> PRT
<213> Homo sapiens

<400> 378
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Met Glu Lys Phe Ile Trp Tyr Leu
20 25 30

Val His Leu Tyr Thr Glu Met Thr Lys Ser Ser Pro Ser Cys Arg Leu
35 40 45

Val Ala Ser Cys Gln Thr Val Ala Lys Glu Leu Gly Glu Asn Ser Leu
50 55 60

Gly Tyr Gly Pro Gly His Tyr Leu Leu Phe Gly Cys Arg Asp Ala Phe
65 70 75 80

Gly Cys Pro Met Pro Gly Leu Phe His Leu Leu Gln Asp Gln Met Ile
85 90 95

Gly Ser Leu His Thr Asp Ser Leu Pro Asn Asp Glu Val Glu Phe Val
100 105 110

Arg Thr Gly Tyr Gly Lys Glu Met Val Lys Val Leu His Ile Gln Arg
115 120 125

Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln Leu
130 135 140

Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp Ile

145 150 155 160

Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys Phe
165 170 175

Lys Glu Asn Asp Pro Ala Asn Ile Asp Gly Ala Met Glu Lys Ala Phe
180 185 190

Cys Phe Phe Leu Gln Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile
195 200 205

Cys Glu His Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val
210 215 220

Tyr Met Glu Glu Ile Pro Trp Lys His Leu Gly Lys Asn Gly Val Lys
225 230 235 240

His Val His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Glu
245 250 255

Val Glu Gln Leu Arg Ser Gly Pro Gln Val Ile His Ser Gly Ile Lys
260 265 270

Asp Leu Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile
275 280 285

Lys Asp Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala
290 295 300

Thr Gln Val Tyr Cys Lys Trp Arg Tyr His Gln Cys Arg Asp Val Asp
305 310 315 320

Phe Lys Ala Thr Trp Asp Thr Ile Arg Asp Leu Val Met Glu Lys Ser
325 330 335

Ala Gly Pro Tyr Asp Lys Gly Glu Tyr Leu Thr Ser Val Gln Lys Thr
340 345 350

Leu Cys Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro Ala Ile Glu
355 360 365

Asp Met Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met
370 375 380

Ser Lys Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp
385 390 395 400

Asn Pro Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser
405 410 415

Arg Leu Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
420 425 430

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
435 440 445

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
450 455 460

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
465 470 475 480

```
Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
                485                 490                 495

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
            500                 505                 510

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
        515                 520                 525

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
    530                 535                 540

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
545                 550                 555                 560

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
                565                 570                 575

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
            580                 585                 590

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
        595                 600                 605

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
    610                 615                 620

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
625                 630                 635                 640

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
                645                 650                 655

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
            660                 665                 670

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
        675                 680                 685

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
    690                 695                 700

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
705                 710                 715                 720

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
                725                 730                 735

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
            740                 745                 750

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
        755                 760                 765

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
    770                 775                 780

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
785                 790                 795                 800
```

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
805 810 815

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
820 825 830

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
835 840 845

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
850 855 860

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
865 870 875 880

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
885 890 895

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
900 905 910

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
915 920 925

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
930 935 940

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
945 950 955 960

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
965 970 975

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
980 985 990

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
995 1000

<210> 379
<211> 928
<212> PRT
<213> Homo sapiens

<400> 379
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Met Pro Val Phe Ser Leu Gln Asn
20 25 30

Asp Glu Val Glu Phe Val Arg Thr Gly Tyr Gly Lys Asp Ile Val Lys
35 40 45

Val Leu His Ile Gln Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val
50 55 60

Ala Thr Ser Val Gln Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His
65 70 75 80

Gly Asp Asn Ser Asp Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val
85 90 95

His Val Leu Ala Lys Phe Lys Glu Asn Glu Pro Ala Asn Ile Asp Gly
100 105 110

Ala Met Glu Lys Ala Phe Cys Phe Phe Leu Gln Ile Lys Ser Ile Glu
115 120 125

Ala Phe Gly Val Asn Ile Cys Glu His Phe Leu Ser Ser Phe Asn His
130 135 140

Val Ile Arg Ala Gln Val Tyr Val Glu Glu Ile Pro Trp Lys His Leu
145 150 155 160

Glu Lys Asn Gly Val Lys His Val His Ala Phe Ile His Thr Pro Thr
165 170 175

Gly Thr His Phe Gly Glu Val Glu Gln Leu Arg Ser Gly Pro Gln Val
180 185 190

Ile His Ser Gly Ile Lys Asp Leu Lys Leu Leu Lys Thr Thr Gln Ser
195 200 205

Gly Phe Glu Gly Phe Ile Lys Asp Gln Phe Thr Thr Leu Pro Glu Val
210 215 220

Phe Lys Cys Met Met Arg Thr Leu Pro Gln Ser Ser Phe Pro Leu Phe
225 230 235 240

Gln Val Leu Ser Met Gly Ser Ser Leu Met Asp Thr Ile Arg Asp Leu
245 250 255

Val Met Glu Lys Ser Ala Gly Pro Tyr Asp Lys Asp Glu Tyr Ser Pro
260 265 270

Ser Val Gln Lys Thr Leu Cys Asp Ile Gln Val Leu Ser Leu Ser Arg
275 280 285

Val Pro Ala Ile Glu Asp Met Glu Ile Ser Leu Pro Asn Ile His Tyr
290 295 300

Phe Asn Ile Asp Met Ser Lys Met Gly Leu Ile Asn Lys Glu Glu Val
305 310 315 320

Leu Leu Pro Leu Asp Asn Pro Tyr Gly Lys Ile Thr Gly Thr Val Lys
325 330 335

Arg Lys Leu Ser Ser Arg Leu Asp Ala His Lys Ser Glu Val Ala His
340 345 350

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
355 360 365

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
370 375 380

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
385 390 395 400

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
405 410 415

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
420 425 430

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
435 440 445

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
450 455 460

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
465 470 475 480

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
485 490 495

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
500 505 510

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
515 520 525

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
530 535 540

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
545 550 555 560

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
565 570 575

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
580 585 590

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
595 600 605

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
610 615 620

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
625 630 635 640

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
645 650 655

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
660 665 670

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
675 680 685

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
690 695 700

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
705 710 715 720

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu

725 730 735

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
740 745 750

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
755 760 765

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
770 775 780

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
785 790 795 800

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
805 810 815

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
820 825 830

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
835 840 845

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
850 855 860

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
865 870 875 880

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
885 890 895

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
900 905 910

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
915 920 925

<210> 380
<211> 913
<212> PRT
<213> Homo sapiens

<400> 380
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Met Ala Asp Tyr His Asn Asn Tyr
20 25 30

Lys Lys Asn Asp Glu Leu Glu Phe Val Arg Thr Gly Tyr Gly Lys Asp
35 40 45

Met Val Lys Val Leu His Ile Gln Arg Asp Gly Lys Tyr His Ser Ile
50 55 60

Lys Glu Val Ala Thr Ser Val Gln Leu Thr Leu Ser Ser Lys Lys Asp
65 70 75 80

Tyr Leu His Gly Asp Asn Ser Asp Ile Ile Pro Thr Asp Thr Ile Lys

85 90 95

Asn Thr Val His Val Leu Ala Lys Phe Lys Gly Ile Lys Ser Ile Glu
100 105 110

Ala Phe Gly Val Asn Ile Cys Glu Tyr Phe Leu Ser Ser Phe Asn His
115 120 125

Val Ile Arg Ala Gln Val Tyr Val Glu Glu Ile Pro Trp Lys Arg Leu
130 135 140

Glu Lys Asn Gly Val Lys His Val His Ala Phe Ile His Thr Pro Thr
145 150 155 160

Gly Thr His Phe Cys Glu Val Glu Gln Leu Arg Ser Gly Pro Pro Val
165 170 175

Ile His Ser Gly Ile Lys Asp Leu Lys Val Leu Lys Thr Thr Gln Ser
180 185 190

Gly Phe Glu Gly Phe Ile Lys Asp Gln Phe Thr Thr Leu Pro Glu Val
195 200 205

Lys Asp Arg Cys Phe Ala Thr Gln Val Tyr Cys Lys Trp Arg Tyr His
210 215 220

Gln Cys Arg Asp Val Asp Phe Glu Ala Thr Trp Gly Thr Ile Arg Asp
225 230 235 240

Leu Val Leu Glu Lys Phe Ala Gly Pro Tyr Asp Lys Gly Glu Tyr Ser
245 250 255

Pro Ser Val Gln Lys Thr Leu Tyr Asp Ile Gln Val Leu Ser Leu Ser
260 265 270

Arg Val Pro Glu Ile Glu Asp Met Glu Ile Ser Leu Pro Asn Ile His
275 280 285

Tyr Phe Asn Ile Asp Met Ser Lys Met Gly Leu Ile Asn Lys Glu Glu
290 295 300

Val Leu Leu Pro Leu Asp Asn Pro Tyr Gly Lys Ile Thr Gly Thr Val
305 310 315 320

Lys Arg Lys Leu Ser Ser Arg Leu Asp Ala His Lys Ser Glu Val Ala
325 330 335

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
340 345 350

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
355 360 365

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
370 375 380

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
385 390 395 400

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
405 410 415

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
420 425 430

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
435 440 445

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
450 455 460

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
465 470 475 480

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
485 490 495

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
500 505 510

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
515 520 525

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
530 535 540

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
545 550 555 560

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
565 570 575

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
580 585 590

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
595 600 605

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
610 615 620

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
625 630 635 640

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
645 650 655

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
660 665 670

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
675 680 685

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
690 695 700

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
705 710 715 720

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
725 730 735

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
740 745 750

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
755 760 765

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
770 775 780

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
785 790 795 800

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
805 810 815

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
820 825 830

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
835 840 845

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
850 855 860

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
865 870 875 880

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
885 890 895

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
900 905 910

Leu

<210> 381
<211> 805
<212> PRT
<213> Homo sapiens

<400> 381
Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1 5 10 15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg Asp Ala His
20 25 30

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
35 40 45

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
50 55 60

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
65 70 75 80

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
85 90 95

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
100 105 110

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
115 120 125

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
130 135 140

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
145 150 155 160

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
165 170 175

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
180 185 190

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
195 200 205

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
210 215 220

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
225 230 235 240

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
245 250 255

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
260 265 270

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
275 280 285

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
290 295 300

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
305 310 315 320

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
325 330 335

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
340 345 350

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
355 360 365

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
370 375 380

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
385 390 395 400

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
405 410 415

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
420 425 430

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
435 440 445

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
450 455 460

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
465 470 475 480

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
485 490 495

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
500 505 510

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
515 520 525

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
530 535 540

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
545 550 555 560

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
565 570 575

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
580 585 590

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
595 600 605

Gln Ala Ala Leu Gly Leu Phe Pro Thr Ile Pro Leu Ser Arg Leu Phe
610 615 620

Asp Asn Ala Met Leu Arg Ala His Arg Leu His Gln Leu Ala Phe Asp
625 630 635 640

Thr Tyr Gln Glu Phe Glu Glu Ala Tyr Ile Pro Lys Glu Gln Lys Tyr
645 650 655

Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu Cys Phe Ser Glu Ser Ile
660 665 670

Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu
675 680 685

Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser Trp Leu Glu Pro Val
690 695 700

Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser
705 710 715 720

Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln
725 730 735

Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile

```
            740                 745                 750

Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp Asp
        755                 760                 765

Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met
    770                 775                 780

Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu
785                 790                 795                 800

Gly Ser Cys Gly Phe
                805


&lt;210&gt; 382
&lt;211&gt; 191
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 382
Phe Pro Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Met Leu Arg
1               5                   10                  15

Ala His Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu
            20                  25                  30

Glu Ala Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro
        35                  40                  45

Gln Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg
    50                  55                  60

Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu
65                  70                  75                  80

Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg Ser Val
                85                  90                  95

Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp
            100                 105                 110

Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu Met Gly Arg Leu
        115                 120                 125

Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe Lys Gln Thr Tyr Ser
    130                 135                 140

Lys Phe Asp Thr Asn Ser His Asn Asp Asp Ala Leu Leu Lys Asn Tyr
145                 150                 155                 160

Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met Asp Lys Val Glu Thr Phe
                165                 170                 175

Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
            180                 185                 190


&lt;210&gt; 383
```

<211> 191
<212> PRT
<213> Homo sapiens

<400> 383
Phe Pro Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Met Leu Arg
1 5 10 15

Ala His Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu
20 25 30

Glu Ala Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro
35 40 45

Gln Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg
50 55 60

Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu
65 70 75 80

Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg Ser Val
85 90 95

Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp
100 105 110

Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu Met Gly Arg Leu
115 120 125

Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe Lys Gln Thr Tyr Ser
130 135 140

Lys Phe Asp Thr Asn Ser His Asn Asp Asp Ala Leu Leu Lys Asn Tyr
145 150 155 160

Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met Asp Lys Val Glu Thr Phe
165 170 175

Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
180 185 190

<210> 384
<211> 191
<212> PRT
<213> Homo sapiens

<400> 384
Phe Pro Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Met Leu Arg
1 5 10 15

Ala His Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu
20 25 30

Glu Ala Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro
35 40 45

Gln Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg
50 55 60

Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu
65 70 75 80

Leu Leu Ile Gln Ser Trp Leu Glu Pro Val Gln Phe Leu Arg Ser Val
85 90 95

Phe Ala Asn Ser Leu Val Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp
100 105 110

Leu Leu Lys Asp Leu Glu Glu Gly Ile Gln Thr Leu Met Gly Arg Leu
115 120 125

Glu Asp Gly Ser Pro Arg Thr Gly Gln Ile Phe Lys Gln Thr Tyr Ser
130 135 140

Lys Phe Asp Thr Asn Ser His Asn Asp Asp Ala Leu Leu Lys Asn Tyr
145 150 155 160

Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met Asp Lys Val Glu Thr Phe
165 170 175

Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly Ser Cys Gly Phe
180 185 190

<210> 385
<211> 165
<212> PRT
<213> Homo sapiens

<400> 385
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

```
Leu Arg Ser Lys Glu
                165



<210> 386
<211> 119
<212> PRT
<213> Homo sapiens

<400> 386
His Ser Asp Pro Ala Arg Arg Gly Glu Leu Ser Val Cys Asp Ser Ile
1               5                   10                  15

Ser Glu Trp Val Thr Ala Ala Asp Lys Lys Thr Ala Val Asp Met Ser
            20                  25                  30

Gly Gly Thr Val Thr Val Leu Glu Lys Val Pro Val Ser Lys Gly Gln
        35                  40                  45

Leu Lys Gln Tyr Phe Tyr Glu Thr Lys Cys Asn Pro Met Gly Tyr Thr
    50                  55                  60

Lys Glu Gly Cys Arg Gly Ile Asp Lys Arg His Trp Asn Ser Gln Cys
65                  70                  75                  80

Arg Thr Thr Gln Ser Tyr Val Arg Ala Leu Thr Met Asp Ser Lys Lys
                85                  90                  95

Arg Ile Gly Trp Arg Phe Ile Arg Ile Asp Thr Ser Cys Val Cys Thr
            100                 105                 110

Leu Thr Ile Lys Arg Gly Arg
        115



<210> 387
<211> 60
<212> PRT
<213> Homo sapiens

<400> 387
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1               5                   10                  15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His Gly
            20                  25                  30

Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala
        35                  40                  45

Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
    50                  55                  60


<210> 388
<211> 32
<212> PRT
<213> Homo sapiens
```

<400> 388
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1   5   10   15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
            20   25   30

<210> 389
<211> 32
<212> PRT
<213> Homo sapiens

<400> 389
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1   5   10   15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
            20   25   30

<210> 390
<211> 60
<212> PRT
<213> Homo sapiens

<400> 390
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1   5   10   15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His Gly
            20   25   30

Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala
        35   40   45

Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
    50   55   60

<210> 391
<211> 29
<212> PRT
<213> Homo sapiens

<400> 391
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1   5   10   15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
            20   25

<210> 392
<211> 32
<212> PRT

<213> Homo sapiens

<400> 392
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 393
<211> 32
<212> PRT
<213> Homo sapiens

<400> 393
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 394
<211> 32
<212> PRT
<213> Homo sapiens

<400> 394
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 395
<211> 32
<212> PRT
<213> Homo sapiens

<400> 395
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 396
<211> 32
<212> PRT
<213> Homo sapiens

<400> 396
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Gly Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 397
<211> 29
<212> PRT
<213> Homo sapiens

<400> 397
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
20 25

<210> 398
<211> 32
<212> PRT
<213> Homo sapiens

<400> 398
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Gly Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 399
<211> 32
<212> PRT
<213> Homo sapiens

<400> 399
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Gly Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 400
<211> 32
<212> PRT
<213> Homo sapiens

<400> 400
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 401
<211> 30
<212> PRT
<213> Homo sapiens

<400> 401
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1   5   10   15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg
            20   25   30

<210> 402
<211> 151
<212> PRT
<213> Homo sapiens

<400> 402
Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1   5   10   15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
            20   25   30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
        35   40   45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
    50   55   60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65   70   75   80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
                85   90   95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
            100   105   110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
        115   120   125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
    130   135   140

Gly Cys Asn Ser Phe Arg Tyr
145   150

<210> 403
<211> 151
<212> PRT
<213> Homo sapiens

<400> 403
Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1   5   10   15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
            20   25   30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
        35   40   45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
50 55 60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65 70 75 80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
85 90 95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
100 105 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
115 120 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
130 135 140

Gly Cys Asn Ser Phe Arg Tyr
145 150

<210> 404
<211> 151
<212> PRT
<213> Homo sapiens

<400> 404
Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1 5 10 15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
20 25 30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
35 40 45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
50 55 60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65 70 75 80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
85 90 95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
100 105 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
115 120 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
130 135 140

Gly Cys Asn Ser Phe Arg Tyr
145 150

<210> 405
<211> 151
<212> PRT
<213> Homo sapiens

<400> 405
Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1 5 10 15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
20 25 30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
35 40 45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
50 55 60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65 70 75 80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
85 90 95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
100 105 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
115 120 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
130 135 140

Gly Cys Asn Ser Phe Arg Tyr
145 150

<210> 406
<211> 151
<212> PRT
<213> Homo sapiens

<400> 406
Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1 5 10 15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
20 25 30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
35 40 45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
50 55 60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65 70 75 80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala

```
                85                  90                  95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
            100                 105                 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
        115                 120                 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
    130                 135                 140

Gly Cys Asn Ser Phe Arg Tyr
145                 150


<210> 407
<211> 151
<212> PRT
<213> Homo sapiens

<400> 407
Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1               5                   10                  15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
            20                  25                  30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
        35                  40                  45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
    50                  55                  60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65                  70                  75                  80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
                85                  90                  95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
            100                 105                 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
        115                 120                 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
    130                 135                 140

Gly Cys Asn Ser Phe Arg Tyr
145                 150


<210> 408
<211> 126
<212> PRT
<213> Homo sapiens

<400> 408
Met His Leu Ser Gln Leu Leu Ala Cys Ala Leu Leu Leu Thr Leu Leu
```

```
1               5                   10                  15

Ser Leu Arg Pro Ser Glu Ala Lys Pro Gly Ala Pro Pro Lys Val Pro
            20                  25                  30

Arg Thr Pro Pro Ala Glu Glu Leu Ala Glu Pro Gln Ala Ala Gly Gly
        35                  40                  45

Gly Gln Lys Lys Gly Asp Lys Ala Pro Gly Gly Gly Gly Ala Asn Leu
    50                  55                  60

Lys Gly Asp Arg Ser Arg Leu Leu Arg Asp Leu Arg Val Asp Thr Lys
65                  70                  75                  80

Ser Arg Ala Ala Trp Ala Arg Leu Leu Gln Glu His Pro Asn Ala Arg
                85                  90                  95

Lys Tyr Lys Gly Ala Asn Lys Lys Gly Leu Ser Lys Gly Cys Phe Gly
            100                 105                 110

Leu Lys Leu Asp Arg Ile Gly Ser Met Ser Gly Leu Gly Cys
        115                 120                 125


<210> 409
<211> 126
<212> PRT
<213> Homo sapiens

<400> 409
Met His Leu Ser Gln Leu Leu Ala Cys Ala Leu Leu Leu Thr Leu Leu
1               5                   10                  15

Ser Leu Arg Pro Ser Glu Ala Lys Pro Gly Ala Pro Pro Lys Val Pro
            20                  25                  30

Arg Thr Pro Pro Ala Glu Glu Leu Ala Glu Pro Gln Ala Ala Gly Gly
        35                  40                  45

Gly Gln Lys Lys Gly Asp Lys Ala Pro Gly Gly Gly Gly Ala Asn Leu
    50                  55                  60

Lys Gly Asp Arg Ser Arg Leu Leu Arg Asp Leu Arg Val Asp Thr Lys
65                  70                  75                  80

Ser Arg Ala Ala Trp Ala Arg Leu Leu Gln Glu His Pro Asn Ala Arg
                85                  90                  95

Lys Tyr Lys Gly Ala Asn Lys Lys Gly Leu Ser Lys Gly Cys Phe Gly
            100                 105                 110

Leu Lys Leu Asp Arg Ile Gly Ser Met Ser Gly Leu Gly Cys
        115                 120                 125


<210> 410
<211> 38
<212> PRT
<213> Dendroaspis angusticeps
```

<400> 410
Glu Val Lys Tyr Asp Pro Cys Phe Gly His Lys Ile Asp Arg Ile Asn
1   5   10   15

His Val Ser Asn Leu Gly Cys Pro Ser Leu Arg Asp Pro Arg Pro Asn
            20   25   30

Ala Pro Ser Thr Ser Ala
        35

<210> 411
<211> 38
<212> PRT
<213> Dendroaspis angusticeps

<400> 411
Glu Val Lys Tyr Asp Pro Cys Phe Gly His Lys Ile Asp Arg Ile Asn
1   5   10   15

His Val Ser Asn Leu Gly Cys Pro Ser Leu Arg Asp Pro Arg Pro Asn
            20   25   30

Ala Pro Ser Thr Ser Ala
        35

<210> 412
<211> 30
<212> PRT
<213> Homo sapiens

<400> 412
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1   5   10   15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg
            20   25   30

<210> 413
<211> 32
<212> PRT
<213> Homo sapiens

<400> 413
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Gly Met Asp
1   5   10   15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
            20   25   30

<210> 414
<211> 32
<212> PRT
<213> Homo sapiens

<400> 414

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Gly Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 415
<211> 32
<212> PRT
<213> Homo sapiens

<400> 415
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Gly Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 416
<211> 32
<212> PRT
<213> Homo sapiens

<400> 416
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Gly Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 417
<211> 303
<212> PRT
<213> Rattus norvegicus

<400> 417
Met Ala His Tyr His Asp Asp Tyr Gly Lys Asn Asp Glu Val Glu Phe
1 5 10 15

Val Arg Thr Gly Tyr Gly Lys Asp Met Val Lys Val Leu His Ile Gln
20 25 30

Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
35 40 45

Leu Thr Leu Arg Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
50 55 60

Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys
65 70 75 80

Phe Lys Gly Ile Lys Ser Ile Glu Thr Phe Ala Met Asn Ile Cys Glu
85 90 95

His Phe Leu Ser Ser Phe Ser His Val Thr Arg Ala His Val Tyr Val
100 105 110

Glu Glu Val Pro Trp Lys Arg Phe Glu Lys Asn Gly Val Lys His Val

```
        115                 120                 125

His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Asp Val Glu
    130                 135                 140

Gln Val Arg Asn Gly Pro Pro Ile Ile His Ser Gly Ile Lys Asp Leu
145                 150                 155                 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
                165                 170                 175

Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
            180                 185                 190

Val Tyr Cys Lys Trp Arg Tyr Gln Asn Arg Asp Val Asp Phe Glu Ala
        195                 200                 205

Thr Trp Gly Ala Val Arg Asp Ile Val Leu Lys Lys Phe Ala Gly Pro
    210                 215                 220

Tyr Asp Arg Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr Asp
225                 230                 235                 240

Ile Gln Val Leu Thr Leu Ser Gln Leu Pro Glu Ile Glu Asp Met Glu
                245                 250                 255

Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met
            260                 265                 270

Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr
        275                 280                 285

Gly Lys Ile Thr Gly Thr Val Arg Arg Lys Leu Pro Ser Arg Leu
    290                 295                 300


<210> 418
<211> 303
<212> PRT
<213> Rattus norvegicus

<400> 418
Met Ala His Tyr His Asp Asp Tyr Gly Lys Asn Asp Glu Val Glu Phe
 1               5                  10                  15

Val Arg Thr Gly Tyr Gly Lys Asp Met Val Lys Val Leu His Ile Gln
            20                  25                  30

Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
        35                  40                  45

Leu Thr Leu Arg Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
    50                  55                  60

Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys
65                  70                  75                  80

Phe Lys Gly Ile Lys Ser Ile Glu Thr Phe Ala Met Asn Ile Cys Glu
                85                  90                  95
```

His Phe Leu Ser Ser Phe Ser His Val Thr Arg Ala His Val Tyr Val
100 105 110

Glu Glu Val Pro Trp Lys Arg Phe Glu Lys Asn Gly Val Lys His Val
115 120 125

His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Asp Val Glu
130 135 140

Gln Val Arg Asn Gly Pro Pro Ile Ile His Ser Gly Ile Lys Asp Leu
145 150 155 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
165 170 175

Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
180 185 190

Val Tyr Cys Lys Trp Arg Tyr Gln Asn Arg Asp Val Asp Phe Glu Ala
195 200 205

Thr Trp Gly Ala Val Arg Asp Ile Val Leu Lys Lys Phe Ala Gly Pro
210 215 220

Tyr Asp Arg Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr Asp
225 230 235 240

Ile Gln Val Leu Thr Leu Ser Gln Leu Pro Glu Ile Glu Asp Met Glu
245 250 255

Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met
260 265 270

Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr
275 280 285

Gly Lys Ile Thr Gly Thr Val Arg Arg Lys Leu Pro Ser Arg Leu
290 295 300

<210> 419
<211> 410
<212> PRT
<213> Mycoplasma arginini

<400> 419
Met Ser Val Phe Asp Ser Lys Phe Lys Gly Ile His Val Tyr Ser Glu
1 5 10 15

Ile Gly Glu Leu Glu Ser Val Leu Val His Glu Pro Gly Arg Glu Ile
20 25 30

Asp Tyr Ile Thr Pro Ala Arg Leu Asp Glu Leu Leu Phe Ser Ala Ile
35 40 45

Leu Glu Ser His Asp Ala Arg Lys Glu His Lys Gln Phe Val Ala Glu
50 55 60

Leu Lys Ala Asn Asp Ile Asn Val Val Glu Leu Ile Asp Leu Val Ala
65 70 75 80

Glu Thr Tyr Asp Leu Ala Ser Gln Glu Ala Lys Asp Lys Leu Ile Glu
85 90 95

Glu Phe Leu Glu Asp Ser Glu Pro Val Leu Ser Glu Glu His Lys Val
100 105 110

Val Val Arg Asn Phe Leu Lys Ala Lys Lys Thr Ser Arg Lys Leu Val
115 120 125

Glu Ile Met Met Ala Gly Ile Thr Lys Tyr Asp Leu Gly Ile Glu Ala
130 135 140

Asp His Glu Leu Ile Val Asp Pro Met Pro Asn Leu Tyr Phe Thr Arg
145 150 155 160

Asp Pro Phe Ala Ser Val Gly Asn Gly Val Thr Ile His Tyr Met Arg
165 170 175

Tyr Lys Val Arg Gln Arg Glu Thr Leu Phe Ser Arg Phe Val Phe Ser
180 185 190

Asn His Pro Lys Leu Ile Asn Thr Pro Trp Tyr Tyr Asp Pro Ser Leu
195 200 205

Lys Leu Ser Ile Glu Gly Gly Asp Val Phe Ile Tyr Asn Asn Asp Thr
210 215 220

Leu Val Val Gly Val Ser Glu Arg Thr Asp Leu Gln Thr Val Thr Leu
225 230 235 240

Leu Ala Lys Asn Ile Val Ala Asn Lys Glu Cys Glu Phe Lys Arg Ile
245 250 255

Val Ala Ile Asn Val Pro Lys Trp Thr Asn Leu Met His Leu Asp Thr
260 265 270

Trp Leu Thr Met Leu Asp Lys Asp Lys Phe Leu Tyr Ser Pro Ile Ala
275 280 285

Asn Asp Val Phe Lys Phe Trp Asp Tyr Asp Leu Val Asn Gly Gly Ala
290 295 300

Glu Pro Gln Pro Val Glu Asn Gly Leu Pro Leu Glu Gly Leu Leu Gln
305 310 315 320

Ser Ile Ile Asn Lys Lys Pro Val Leu Ile Pro Ile Ala Gly Glu Gly
325 330 335

Ala Ser Gln Met Glu Ile Glu Arg Glu Thr His Phe Asp Gly Thr Asn
340 345 350

Tyr Leu Ala Ile Arg Pro Gly Val Val Ile Gly Tyr Ser Arg Asn Glu
355 360 365

Lys Thr Asn Ala Ala Leu Glu Ala Ala Gly Ile Lys Val Leu Pro Phe
370 375 380

His Gly Asn Gln Leu Ser Leu Gly Met Gly Asn Ala Arg Cys Met Ser
385 390 395 400

Met Pro Leu Ser Arg Lys Asp Val Lys Trp

405 410

<210> 420
<211> 410
<212> PRT
<213> Mycoplasma arginini

<400> 420
Met Ser Val Phe Asp Ser Lys Phe Lys Gly Ile His Val Tyr Ser Glu
1 5 10 15

Ile Gly Glu Leu Glu Ser Val Leu Val His Glu Pro Gly Arg Glu Ile
20 25 30

Asp Tyr Ile Thr Pro Ala Arg Leu Asp Glu Leu Leu Phe Ser Ala Ile
35 40 45

Leu Glu Ser His Asp Ala Arg Lys Glu His Lys Gln Phe Val Ala Glu
50 55 60

Leu Lys Ala Asn Asp Ile Asn Val Val Glu Leu Ile Asp Leu Val Ala
65 70 75 80

Glu Thr Tyr Asp Leu Ala Ser Gln Glu Ala Lys Asp Lys Leu Ile Glu
85 90 95

Glu Phe Leu Glu Asp Ser Glu Pro Val Leu Ser Glu Glu His Lys Val
100 105 110

Val Val Arg Asn Phe Leu Lys Ala Lys Lys Thr Ser Arg Lys Leu Val
115 120 125

Glu Ile Met Met Ala Gly Ile Thr Lys Tyr Asp Leu Gly Ile Glu Ala
130 135 140

Asp His Glu Leu Ile Val Asp Pro Met Pro Asn Leu Tyr Phe Thr Arg
145 150 155 160

Asp Pro Phe Ala Ser Val Gly Asn Gly Val Thr Ile His Tyr Met Arg
165 170 175

Tyr Lys Val Arg Gln Arg Glu Thr Leu Phe Ser Arg Phe Val Phe Ser
180 185 190

Asn His Pro Lys Leu Ile Asn Thr Pro Trp Tyr Tyr Asp Pro Ser Leu
195 200 205

Lys Leu Ser Ile Glu Gly Gly Asp Val Phe Ile Tyr Asn Asn Asp Thr
210 215 220

Leu Val Val Gly Val Ser Glu Arg Thr Asp Leu Gln Thr Val Thr Leu
225 230 235 240

Leu Ala Lys Asn Ile Val Ala Asn Lys Glu Cys Glu Phe Lys Arg Ile
245 250 255

Val Ala Ile Asn Val Pro Lys Trp Thr Asn Leu Met His Leu Asp Thr
260 265 270

```
Trp Leu Thr Met Leu Asp Lys Asp Lys Phe Leu Tyr Ser Pro Ile Ala
        275                 280                 285

Asn Asp Val Phe Lys Phe Trp Asp Tyr Asp Leu Val Asn Gly Gly Ala
    290                 295                 300

Glu Pro Gln Pro Val Glu Asn Gly Leu Pro Leu Glu Gly Leu Leu Gln
305                 310                 315                 320

Ser Ile Ile Asn Lys Lys Pro Val Leu Ile Pro Ile Ala Gly Glu Gly
                325                 330                 335

Ala Ser Gln Met Glu Ile Glu Arg Glu Thr His Phe Asp Gly Thr Asn
            340                 345                 350

Tyr Leu Ala Ile Arg Pro Gly Val Val Ile Gly Tyr Ser Arg Asn Glu
        355                 360                 365

Lys Thr Asn Ala Ala Leu Glu Ala Ala Gly Ile Lys Val Leu Pro Phe
    370                 375                 380

His Gly Asn Gln Leu Ser Leu Gly Met Gly Asn Ala Arg Cys Met Ser
385                 390                 395                 400

Met Pro Leu Ser Arg Lys Asp Val Lys Trp
                405                 410


<210> 421
<211> 410
<212> PRT
<213> Mycoplasma arginini

<400> 421
Met Ser Val Phe Asp Ser Lys Phe Lys Gly Ile His Val Tyr Ser Glu
1               5                   10                  15

Ile Gly Glu Leu Glu Ser Val Leu Val His Glu Pro Gly Arg Glu Ile
            20                  25                  30

Asp Tyr Ile Thr Pro Ala Arg Leu Asp Glu Leu Leu Phe Ser Ala Ile
        35                  40                  45

Leu Glu Ser His Asp Ala Arg Lys Glu His Lys Gln Phe Val Ala Glu
    50                  55                  60

Leu Lys Ala Asn Asp Ile Asn Val Val Glu Leu Ile Asp Leu Val Ala
65                  70                  75                  80

Glu Thr Tyr Asp Leu Ala Ser Gln Glu Ala Lys Asp Lys Leu Ile Glu
                85                  90                  95

Glu Phe Leu Glu Asp Ser Glu Pro Val Leu Ser Glu Glu His Lys Val
            100                 105                 110

Val Val Arg Asn Phe Leu Lys Ala Lys Lys Thr Ser Arg Lys Leu Val
        115                 120                 125

Glu Ile Met Met Ala Gly Ile Thr Lys Tyr Asp Leu Gly Ile Glu Ala
    130                 135                 140
```

Asp His Glu Leu Ile Val Asp Pro Met Pro Asn Leu Tyr Phe Thr Arg
145 150 155 160

Asp Pro Phe Ala Ser Val Gly Asn Gly Val Thr Ile His Tyr Met Arg
165 170 175

Tyr Lys Val Arg Gln Arg Glu Thr Leu Phe Ser Arg Phe Val Phe Ser
180 185 190

Asn His Pro Lys Leu Ile Asn Thr Pro Trp Tyr Tyr Asp Pro Ser Leu
195 200 205

Lys Leu Ser Ile Glu Gly Gly Asp Val Phe Ile Tyr Asn Asn Asp Thr
210 215 220

Leu Val Val Gly Val Ser Glu Arg Thr Asp Leu Gln Thr Val Thr Leu
225 230 235 240

Leu Ala Lys Asn Ile Val Ala Asn Lys Glu Cys Glu Phe Lys Arg Ile
245 250 255

Val Ala Ile Asn Val Pro Lys Trp Thr Asn Leu Met His Leu Asp Thr
260 265 270

Trp Leu Thr Met Leu Asp Lys Asp Lys Phe Leu Tyr Ser Pro Ile Ala
275 280 285

Asn Asp Val Phe Lys Phe Trp Asp Tyr Asp Leu Val Asn Gly Gly Ala
290 295 300

Glu Pro Gln Pro Val Glu Asn Gly Leu Pro Leu Glu Gly Leu Leu Gln
305 310 315 320

Ser Ile Ile Asn Lys Lys Pro Val Leu Ile Pro Ile Ala Gly Glu Gly
325 330 335

Ala Ser Gln Met Glu Ile Glu Arg Glu Thr His Phe Asp Gly Thr Asn
340 345 350

Tyr Leu Ala Ile Arg Pro Gly Val Val Ile Gly Tyr Ser Arg Asn Glu
355 360 365

Lys Thr Asn Ala Ala Leu Glu Ala Ala Gly Ile Lys Val Leu Pro Phe
370 375 380

His Gly Asn Gln Leu Ser Leu Gly Met Gly Asn Ala Arg Cys Met Ser
385 390 395 400

Met Pro Leu Ser Arg Lys Asp Val Lys Trp
405 410

<210> 422
<211> 410
<212> PRT
<213> Mycoplasma arginini

<400> 422
Met Ser Val Phe Asp Ser Lys Phe Lys Gly Ile His Val Tyr Ser Glu

1 5 10 15

Ile Gly Glu Leu Glu Ser Val Leu Val His Glu Pro Gly Arg Glu Ile
20 25 30

Asp Tyr Ile Thr Pro Ala Arg Leu Asp Glu Leu Leu Phe Ser Ala Ile
35 40 45

Leu Glu Ser His Asp Ala Arg Lys Glu His Lys Gln Phe Val Ala Glu
50 55 60

Leu Lys Ala Asn Asp Ile Asn Val Val Glu Leu Ile Asp Leu Val Ala
65 70 75 80

Glu Thr Tyr Asp Leu Ala Ser Gln Glu Ala Lys Asp Lys Leu Ile Glu
85 90 95

Glu Phe Leu Glu Asp Ser Glu Pro Val Leu Ser Glu Glu His Lys Val
100 105 110

Val Val Arg Asn Phe Leu Lys Ala Lys Lys Thr Ser Arg Lys Leu Val
115 120 125

Glu Ile Met Met Ala Gly Ile Thr Lys Tyr Asp Leu Gly Ile Glu Ala
130 135 140

Asp His Glu Leu Ile Val Asp Pro Met Pro Asn Leu Tyr Phe Thr Arg
145 150 155 160

Asp Pro Phe Ala Ser Val Gly Asn Gly Val Thr Ile His Tyr Met Arg
165 170 175

Tyr Lys Val Arg Gln Arg Glu Thr Leu Phe Ser Arg Phe Val Phe Ser
180 185 190

Asn His Pro Lys Leu Ile Asn Thr Pro Trp Tyr Tyr Asp Pro Ser Leu
195 200 205

Lys Leu Ser Ile Glu Gly Gly Asp Val Phe Ile Tyr Asn Asn Asp Thr
210 215 220

Leu Val Val Gly Val Ser Glu Arg Thr Asp Leu Gln Thr Val Thr Leu
225 230 235 240

Leu Ala Lys Asn Ile Val Ala Asn Lys Glu Cys Glu Phe Lys Arg Ile
245 250 255

Val Ala Ile Asn Val Pro Lys Trp Thr Asn Leu Met His Leu Asp Thr
260 265 270

Trp Leu Thr Met Leu Asp Lys Asp Lys Phe Leu Tyr Ser Pro Ile Ala
275 280 285

Asn Asp Val Phe Lys Phe Trp Asp Tyr Asp Leu Val Asn Gly Gly Ala
290 295 300

Glu Pro Gln Pro Val Glu Asn Gly Leu Pro Leu Glu Gly Leu Leu Gln
305 310 315 320

Ser Ile Ile Asn Lys Lys Pro Val Leu Ile Pro Ile Ala Gly Glu Gly
325 330 335

Ala Ser Gln Met Glu Ile Glu Arg Glu Thr His Phe Asp Gly Thr Asn
340 345 350

Tyr Leu Ala Ile Arg Pro Gly Val Val Ile Gly Tyr Ser Arg Asn Glu
355 360 365

Lys Thr Asn Ala Ala Leu Glu Ala Ala Gly Ile Lys Val Leu Pro Phe
370 375 380

His Gly Asn Gln Leu Ser Leu Gly Met Gly Asn Ala Arg Cys Met Ser
385 390 395 400

Met Pro Leu Ser Arg Lys Asp Val Lys Trp
405 410

<210> 423
<211> 129
<212> PRT
<213> Homo sapiens

<400> 423
Met Ala Arg Gly Ser Leu Arg Arg Leu Leu Arg Leu Leu Val Leu Gly
1 5 10 15

Leu Trp Leu Ala Leu Leu Arg Ser Val Ala Gly Glu Gln Ala Pro Gly
20 25 30

Thr Ala Pro Cys Ser Arg Gly Ser Ser Trp Ser Ala Asp Leu Asp Lys
35 40 45

Cys Met Asp Cys Ala Ser Cys Arg Ala Arg Pro His Ser Asp Phe Cys
50 55 60

Leu Gly Cys Ala Ala Ala Pro Pro Ala Pro Phe Arg Leu Leu Trp Pro
65 70 75 80

Ile Leu Gly Gly Ala Leu Ser Leu Thr Phe Val Leu Gly Leu Leu Ser
85 90 95

Gly Phe Leu Val Trp Arg Arg Cys Arg Arg Arg Glu Lys Phe Thr Thr
100 105 110

Pro Ile Glu Glu Thr Gly Gly Glu Gly Cys Pro Ala Val Ala Leu Ile
115 120 125

Gln

<210> 424
<211> 497
<212> PRT
<213> Homo sapiens

<400> 424
Ala Arg Pro Cys Ile Pro Lys Ser Phe Gly Tyr Ser Ser Val Val Cys
1 5 10 15

Val Cys Asn Ala Thr Tyr Cys Asp Ser Phe Asp Pro Pro Thr Phe Pro

20 25 30

Ala Leu Gly Thr Phe Ser Arg Tyr Glu Ser Thr Arg Ser Gly Arg Arg
35 40 45

Met Glu Leu Ser Met Gly Pro Ile Gln Ala Asn His Thr Gly Thr Gly
50 55 60

Leu Leu Leu Thr Leu Gln Pro Glu Gln Lys Phe Gln Lys Val Lys Gly
65 70 75 80

Phe Gly Gly Ala Met Thr Asp Ala Ala Ala Leu Asn Ile Leu Ala Leu
85 90 95

Ser Pro Pro Ala Gln Asn Leu Leu Leu Lys Ser Tyr Phe Ser Glu Glu
100 105 110

Gly Ile Gly Tyr Asn Ile Ile Arg Val Pro Met Ala Ser Cys Asp Phe
115 120 125

Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro Asp Asp Phe Gln Leu
130 135 140

His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys Leu Lys Ile Pro Leu
145 150 155 160

Ile His Arg Ala Leu Gln Leu Ala Gln Arg Pro Val Ser Leu Leu Ala
165 170 175

Ser Pro Trp Thr Ser Pro Thr Trp Leu Lys Thr Asn Gly Ala Val Asn
180 185 190

Gly Lys Gly Ser Leu Lys Gly Gln Pro Gly Asp Ile Tyr His Gln Thr
195 200 205

Trp Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala Tyr Ala Glu His Lys
210 215 220

Leu Gln Phe Trp Ala Val Thr Ala Glu Asn Glu Pro Ser Ala Gly Leu
225 230 235 240

Leu Ser Gly Tyr Pro Phe Gln Cys Leu Gly Phe Thr Pro Glu His Gln
245 250 255

Arg Asp Phe Ile Ala Arg Asp Leu Gly Pro Thr Leu Ala Asn Ser Thr
260 265 270

His His Asn Val Arg Leu Leu Met Leu Asp Asp Gln Arg Leu Leu Leu
275 280 285

Pro His Trp Ala Lys Val Val Leu Thr Asp Pro Glu Ala Ala Lys Tyr
290 295 300

Val His Gly Ile Ala Val His Trp Tyr Leu Asp Phe Leu Ala Pro Ala
305 310 315 320

Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe Pro Asn Thr Met Leu
325 330 335

Phe Ala Ser Glu Ala Cys Val Gly Ser Lys Phe Trp Glu Gln Ser Val
340 345 350

```
Arg Leu Gly Ser Trp Asp Arg Gly Met Gln Tyr Ser His Ser Ile Ile
        355                 360                 365

Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr Asp Trp Asn Leu Ala
    370                 375                 380

Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg Asn Phe Val Asp Ser
385                 390                 395                 400

Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe Tyr Lys Gln Pro Met
                405                 410                 415

Phe Tyr His Leu Gly His Phe Ser Lys Phe Ile Pro Glu Gly Ser Gln
            420                 425                 430

Arg Val Gly Leu Val Ala Ser Gln Lys Asn Asp Leu Asp Ala Val Ala
        435                 440                 445

Leu Met His Pro Asp Gly Ser Ala Val Val Val Val Leu Asn Arg Ser
    450                 455                 460

Ser Lys Asp Val Pro Leu Thr Ile Lys Asp Pro Ala Val Gly Phe Leu
465                 470                 475                 480

Glu Thr Ile Ser Pro Gly Tyr Ser Ile His Thr Tyr Leu Trp Arg Arg
                485                 490                 495

Gln


<210> 425
<211> 497
<212> PRT
<213> Homo sapiens

<400> 425
Ala Arg Pro Cys Ile Pro Lys Ser Phe Gly Tyr Ser Ser Val Val Cys
1               5                   10                  15

Val Cys Asn Ala Thr Tyr Cys Asp Ser Phe Asp Pro Pro Thr Phe Pro
            20                  25                  30

Ala Leu Gly Thr Phe Ser Arg Tyr Glu Ser Thr Arg Ser Gly Arg Arg
        35                  40                  45

Met Glu Leu Ser Met Gly Pro Ile Gln Ala Asn His Thr Gly Thr Gly
    50                  55                  60

Leu Leu Leu Thr Leu Gln Pro Glu Gln Lys Phe Gln Lys Val Lys Gly
65                  70                  75                  80

Phe Gly Gly Ala Met Thr Asp Ala Ala Ala Leu Asn Ile Leu Ala Leu
                85                  90                  95

Ser Pro Pro Ala Gln Asn Leu Leu Leu Lys Ser Tyr Phe Ser Glu Glu
            100                 105                 110

Gly Ile Gly Tyr Asn Ile Ile Arg Val Pro Met Ala Ser Cys Asp Phe
        115                 120                 125
```

Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro Asp Asp Phe Gln Leu
    130   135   140

His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys Leu Lys Ile Pro Leu
145   150   155   160

Ile His Arg Ala Leu Gln Leu Ala Gln Arg Pro Val Ser Leu Leu Ala
                165   170   175

Ser Pro Trp Thr Ser Pro Thr Trp Leu Lys Thr Asn Gly Ala Val Asn
            180   185   190

Gly Lys Gly Ser Leu Lys Gly Gln Pro Gly Asp Ile Tyr His Gln Thr
        195   200   205

Trp Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala Tyr Ala Glu His Lys
    210   215   220

Leu Gln Phe Trp Ala Val Thr Ala Glu Asn Glu Pro Ser Ala Gly Leu
225   230   235   240

Leu Ser Gly Tyr Pro Phe Gln Cys Leu Gly Phe Thr Pro Glu His Gln
                245   250   255

Arg Asp Phe Ile Ala Arg Asp Leu Gly Pro Thr Leu Ala Asn Ser Thr
            260   265   270

His His Asn Val Arg Leu Leu Met Leu Asp Asp Gln Arg Leu Leu Leu
        275   280   285

Pro His Trp Ala Lys Val Val Leu Thr Asp Pro Glu Ala Ala Lys Tyr
    290   295   300

Val His Gly Ile Ala Val His Trp Tyr Leu Asp Phe Leu Ala Pro Ala
305   310   315   320

Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe Pro Asn Thr Met Leu
                325   330   335

Phe Ala Ser Glu Ala Cys Val Gly Ser Lys Phe Trp Glu Gln Ser Val
            340   345   350

Arg Leu Gly Ser Trp Asp Arg Gly Met Gln Tyr Ser His Ser Ile Ile
        355   360   365

Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr Asp Trp Asn Leu Ala
    370   375   380

Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg Asn Phe Val Asp Ser
385   390   395   400

Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe Tyr Lys Gln Pro Met
                405   410   415

Phe Tyr His Leu Gly His Phe Ser Lys Phe Ile Pro Glu Gly Ser Gln
            420   425   430

Arg Val Gly Leu Val Ala Ser Gln Lys Asn Asp Leu Asp Ala Val Ala
        435   440   445

Leu Met His Pro Asp Gly Ser Ala Val Val Val Val Leu Asn Arg Ser

450 455 460

Ser Lys Asp Val Pro Leu Thr Ile Lys Asp Pro Ala Val Gly Phe Leu
465 470 475 480

Glu Thr Ile Ser Pro Gly Tyr Ser Ile His Thr Tyr Leu Trp Arg Arg
485 490 495

Gln

<210> 426
<211> 497
<212> PRT
<213> Homo sapiens

<400> 426
Ala Arg Pro Cys Ile Pro Lys Ser Phe Gly Tyr Ser Ser Val Val Cys
1 5 10 15

Val Cys Asn Ala Thr Tyr Cys Asp Ser Phe Asp Pro Pro Thr Phe Pro
20 25 30

Ala Leu Gly Thr Phe Ser Arg Tyr Glu Ser Thr Arg Ser Gly Arg Arg
35 40 45

Met Glu Leu Ser Met Gly Pro Ile Gln Ala Asn His Thr Gly Thr Gly
50 55 60

Leu Leu Leu Thr Leu Gln Pro Glu Gln Lys Phe Gln Lys Val Lys Gly
65 70 75 80

Phe Gly Gly Ala Met Thr Asp Ala Ala Ala Leu Asn Ile Leu Ala Leu
85 90 95

Ser Pro Pro Ala Gln Asn Leu Leu Leu Lys Ser Tyr Phe Ser Glu Glu
100 105 110

Gly Ile Gly Tyr Asn Ile Ile Arg Val Pro Met Ala Ser Cys Asp Phe
115 120 125

Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro Asp Asp Phe Gln Leu
130 135 140

His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys Leu Lys Ile Pro Leu
145 150 155 160

Ile His Arg Ala Leu Gln Leu Ala Gln Arg Pro Val Ser Leu Leu Ala
165 170 175

Ser Pro Trp Thr Ser Pro Thr Trp Leu Lys Thr Asn Gly Ala Val Asn
180 185 190

Gly Lys Gly Ser Leu Lys Gly Gln Pro Gly Asp Ile Tyr His Gln Thr
195 200 205

Trp Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala Tyr Ala Glu His Lys
210 215 220

Leu Gln Phe Trp Ala Val Thr Ala Glu Asn Glu Pro Ser Ala Gly Leu

225 230 235 240

Leu Ser Gly Tyr Pro Phe Gln Cys Leu Gly Phe Thr Pro Glu His Gln
245 250 255

Arg Asp Phe Ile Ala Arg Asp Leu Gly Pro Thr Leu Ala Asn Ser Thr
260 265 270

His His Asn Val Arg Leu Leu Met Leu Asp Asp Gln Arg Leu Leu Leu
275 280 285

Pro His Trp Ala Lys Val Val Leu Thr Asp Pro Glu Ala Ala Lys Tyr
290 295 300

Val His Gly Ile Ala Val His Trp Tyr Leu Asp Phe Leu Ala Pro Ala
305 310 315 320

Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe Pro Asn Thr Met Leu
325 330 335

Phe Ala Ser Glu Ala Cys Val Gly Ser Lys Phe Trp Glu Gln Ser Val
340 345 350

Arg Leu Gly Ser Trp Asp Arg Gly Met Gln Tyr Ser His Ser Ile Ile
355 360 365

Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr Asp Trp Asn Leu Ala
370 375 380

Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg Asn Phe Val Asp Ser
385 390 395 400

Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe Tyr Lys Gln Pro Met
405 410 415

Phe Tyr His Leu Gly His Phe Ser Lys Phe Ile Pro Glu Gly Ser Gln
420 425 430

Arg Val Gly Leu Val Ala Ser Gln Lys Asn Asp Leu Asp Ala Val Ala
435 440 445

Leu Met His Pro Asp Gly Ser Ala Val Val Val Val Leu Asn Arg Ser
450 455 460

Ser Lys Asp Val Pro Leu Thr Ile Lys Asp Pro Ala Val Gly Phe Leu
465 470 475 480

Glu Thr Ile Ser Pro Gly Tyr Ser Ile His Thr Tyr Leu Trp Arg Arg
485 490 495

Gln

<210> 427
<211> 497
<212> PRT
<213> Homo sapiens

<400> 427
Ala Arg Pro Cys Ile Pro Lys Ser Phe Gly Tyr Ser Ser Val Val Cys

1 5 10 15

Val Cys Asn Ala Thr Tyr Cys Asp Ser Phe Asp Pro Pro Thr Phe Pro
20 25 30

Ala Leu Gly Thr Phe Ser Arg Tyr Glu Ser Thr Arg Ser Gly Arg Arg
35 40 45

Met Glu Leu Ser Met Gly Pro Ile Gln Ala Asn His Thr Gly Thr Gly
50 55 60

Leu Leu Leu Thr Leu Gln Pro Glu Gln Lys Phe Gln Lys Val Lys Gly
65 70 75 80

Phe Gly Gly Ala Met Thr Asp Ala Ala Ala Leu Asn Ile Leu Ala Leu
85 90 95

Ser Pro Pro Ala Gln Asn Leu Leu Leu Lys Ser Tyr Phe Ser Glu Glu
100 105 110

Gly Ile Gly Tyr Asn Ile Ile Arg Val Pro Met Ala Ser Cys Asp Phe
115 120 125

Ser Ile Arg Thr Tyr Thr Tyr Ala Asp Thr Pro Asp Asp Phe Gln Leu
130 135 140

His Asn Phe Ser Leu Pro Glu Glu Asp Thr Lys Leu Lys Ile Pro Leu
145 150 155 160

Ile His Arg Ala Leu Gln Leu Ala Gln Arg Pro Val Ser Leu Leu Ala
165 170 175

Ser Pro Trp Thr Ser Pro Thr Trp Leu Lys Thr Asn Gly Ala Val Asn
180 185 190

Gly Lys Gly Ser Leu Lys Gly Gln Pro Gly Asp Ile Tyr His Gln Thr
195 200 205

Trp Ala Arg Tyr Phe Val Lys Phe Leu Asp Ala Tyr Ala Glu His Lys
210 215 220

Leu Gln Phe Trp Ala Val Thr Ala Glu Asn Glu Pro Ser Ala Gly Leu
225 230 235 240

Leu Ser Gly Tyr Pro Phe Gln Cys Leu Gly Phe Thr Pro Glu His Gln
245 250 255

Arg Asp Phe Ile Ala Arg Asp Leu Gly Pro Thr Leu Ala Asn Ser Thr
260 265 270

His His Asn Val Arg Leu Leu Met Leu Asp Asp Gln Arg Leu Leu Leu
275 280 285

Pro His Trp Ala Lys Val Val Leu Thr Asp Pro Glu Ala Ala Lys Tyr
290 295 300

Val His Gly Ile Ala Val His Trp Tyr Leu Asp Phe Leu Ala Pro Ala
305 310 315 320

Lys Ala Thr Leu Gly Glu Thr His Arg Leu Phe Pro Asn Thr Met Leu
325 330 335

Phe Ala Ser Glu Ala Cys Val Gly Ser Lys Phe Trp Glu Gln Ser Val
340 345 350

Arg Leu Gly Ser Trp Asp Arg Gly Met Gln Tyr Ser His Ser Ile Ile
355 360 365

Thr Asn Leu Leu Tyr His Val Val Gly Trp Thr Asp Trp Asn Leu Ala
370 375 380

Leu Asn Pro Glu Gly Gly Pro Asn Trp Val Arg Asn Phe Val Asp Ser
385 390 395 400

Pro Ile Ile Val Asp Ile Thr Lys Asp Thr Phe Tyr Lys Gln Pro Met
405 410 415

Phe Tyr His Leu Gly His Phe Ser Lys Phe Ile Pro Glu Gly Ser Gln
420 425 430

Arg Val Gly Leu Val Ala Ser Gln Lys Asn Asp Leu Asp Ala Val Ala
435 440 445

Leu Met His Pro Asp Gly Ser Ala Val Val Val Val Leu Asn Arg Ser
450 455 460

Ser Lys Asp Val Pro Leu Thr Ile Lys Asp Pro Ala Val Gly Phe Leu
465 470 475 480

Glu Thr Ile Ser Pro Gly Tyr Ser Ile His Thr Tyr Leu Trp Arg Arg
485 490 495

Gln

<210> 428
<211> 52
<212> PRT
<213> Homo sapiens

<400> 428
Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly Cys
1 5 10 15

Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr Gln
20 25 30

Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile Ser
35 40 45

Pro Gln Gly Tyr
50

<210> 429
<211> 52
<212> PRT
<213> Homo sapiens

<400> 429
Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly Cys
1 5 10 15

Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr Gln
20 25 30

Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile Ser
35 40 45

Pro Gln Gly Tyr
50

<210> 430
<211> 52
<212> PRT
<213> Homo sapiens

<400> 430
Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly Cys
1 5 10 15

Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr Gln
20 25 30

Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile Ser
35 40 45

Pro Gln Gly Tyr
50

<210> 431
<211> 52
<212> PRT
<213> Homo sapiens

<400> 431
Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly Cys
1 5 10 15

Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr Gln
20 25 30

Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile Ser
35 40 45

Pro Gln Gly Tyr
50

<210> 432
<211> 145
<212> PRT
<213> Homo sapiens

<400> 432
Met Asn Ser Leu Val Ser Trp Gln Leu Leu Leu Phe Leu Cys Ala Thr
1 5 10 15

His Phe Gly Glu Pro Leu Glu Lys Val Ala Ser Val Gly Asn Ser Arg
20 25 30

Pro Thr Gly Gln Gln Leu Glu Ser Leu Gly Leu Leu Ala Pro Gly Glu
35 40 45

Gln Ser Leu Pro Cys Thr Glu Arg Lys Pro Ala Ala Thr Ala Arg Leu
50 55 60

Ser Arg Arg Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser
65 70 75 80

Pro Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala
85 90 95

Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr
100 105 110

Asn Trp Asn Ser Phe Gly Leu Arg Phe Gly Lys Arg Glu Ala Ala Pro
115 120 125

Gly Asn His Gly Arg Ser Ala Gly Arg Gly Trp Gly Ala Gly Ala Gly
130 135 140

Gln
145

<210> 433
<211> 145
<212> PRT
<213> Homo sapiens

<400> 433
Met Asn Ser Leu Val Ser Trp Gln Leu Leu Leu Phe Leu Cys Ala Thr
1 5 10 15

His Phe Gly Glu Pro Leu Glu Lys Val Ala Ser Val Gly Asn Ser Arg
20 25 30

Pro Thr Gly Gln Gln Leu Glu Ser Leu Gly Leu Leu Ala Pro Gly Glu
35 40 45

Gln Ser Leu Pro Cys Thr Glu Arg Lys Pro Ala Ala Thr Ala Arg Leu
50 55 60

Ser Arg Arg Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser
65 70 75 80

Pro Gln Gln Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala
85 90 95

Pro Gln Gly Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr
100 105 110

Asn Trp Asn Ser Phe Gly Leu Arg Phe Gly Lys Arg Glu Ala Ala Pro
115 120 125

Gly Asn His Gly Arg Ser Ala Gly Arg Gly Trp Gly Ala Gly Ala Gly
130 135 140

Gln
145

```
<210> 434
<211> 346
<212> PRT
<213> Homo sapiens

<400> 434
Met Ala Arg Pro Gly Gln Arg Trp Leu Gly Lys Trp Leu Val Ala Met
1               5                   10                  15

Val Val Trp Ala Leu Cys Arg Leu Ala Thr Pro Leu Ala Lys Asn Leu
            20                  25                  30

Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe Leu Ser Gly Lys
        35                  40                  45

Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu Asp Ile Ile Cys
    50                  55                  60

Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr Lys Leu Tyr Leu
65                  70                  75                  80

Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val Leu Asp Pro Asn
                85                  90                  95

Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile Arg Phe Thr Ile
            100                 105                 110

Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu Glu Phe Lys Lys
        115                 120                 125

His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly Ser Leu Glu Gly
    130                 135                 140

Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg Thr Met Lys Ile
145                 150                 155                 160

Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr Pro Glu Gln Leu
                165                 170                 175

Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr Val Lys Met Ala
            180                 185                 190

Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp Ser Asp Gly Lys
        195                 200                 205

His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro Gly Ala Ser Gly
    210                 215                 220

Gly Ser Ser Gly Asp Pro Asp Gly Phe Phe Asn Ser Lys Val Ala Leu
225                 230                 235                 240

Phe Ala Ala Val Gly Ala Gly Cys Val Ile Phe Leu Leu Ile Ile Ile
                245                 250                 255

Phe Leu Thr Val Leu Leu Leu Lys Leu Arg Lys Arg His Arg Lys His
            260                 265                 270

Thr Gln Gln Arg Ala Ala Ala Leu Ser Leu Ser Thr Leu Ala Ser Pro
        275                 280                 285
```

Lys Gly Gly Ser Gly Thr Ala Gly Thr Glu Pro Ser Asp Ile Ile Ile
    290   295   300

Pro Leu Arg Thr Thr Glu Asn Asn Tyr Cys Pro His Tyr Glu Lys Val
305   310   315   320

Ser Gly Asp Tyr Gly His Pro Val Tyr Ile Val Gln Glu Met Pro Pro
                325   330   335

Gln Ser Pro Ala Asn Ile Tyr Tyr Lys Val
            340   345

<210> 435
<211> 346
<212> PRT
<213> Homo sapiens

<400> 435
Met Ala Arg Pro Gly Gln Arg Trp Leu Gly Lys Trp Leu Val Ala Met
1   5   10   15

Val Val Trp Ala Leu Cys Arg Leu Ala Thr Pro Leu Ala Lys Asn Leu
            20   25   30

Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe Leu Ser Gly Lys
        35   40   45

Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu Asp Ile Ile Cys
    50   55   60

Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr Lys Leu Tyr Leu
65   70   75   80

Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val Leu Asp Pro Asn
                85   90   95

Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile Arg Phe Thr Ile
            100   105   110

Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu Glu Phe Lys Lys
        115   120   125

His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly Ser Leu Glu Gly
    130   135   140

Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg Thr Met Lys Ile
145   150   155   160

Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr Pro Glu Gln Leu
                165   170   175

Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr Val Lys Met Ala
            180   185   190

Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp Ser Asp Gly Lys
        195   200   205

His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro Gly Ala Ser Gly
    210   215   220

Gly Ser Ser Gly Asp Pro Asp Gly Phe Phe Asn Ser Lys Val Ala Leu
225 230 235 240

Phe Ala Ala Val Gly Ala Gly Cys Val Ile Phe Leu Leu Ile Ile Ile
245 250 255

Phe Leu Thr Val Leu Leu Leu Lys Leu Arg Lys Arg His Arg Lys His
260 265 270

Thr Gln Gln Arg Ala Ala Ala Leu Ser Leu Ser Thr Leu Ala Ser Pro
275 280 285

Lys Gly Gly Ser Gly Thr Ala Gly Thr Glu Pro Ser Asp Ile Ile Ile
290 295 300

Pro Leu Arg Thr Thr Glu Asn Asn Tyr Cys Pro His Tyr Glu Lys Val
305 310 315 320

Ser Gly Asp Tyr Gly His Pro Val Tyr Ile Val Gln Glu Met Pro Pro
325 330 335

Gln Ser Pro Ala Asn Ile Tyr Tyr Lys Val
340 345

<210> 436
<211> 129
<212> PRT
<213> Homo sapiens

<400> 436
Met Ala Arg Gly Ser Leu Arg Arg Leu Leu Arg Leu Leu Val Leu Gly
1 5 10 15

Leu Trp Leu Ala Leu Leu Arg Ser Val Ala Gly Glu Gln Ala Pro Gly
20 25 30

Thr Ala Pro Cys Ser Arg Gly Ser Ser Trp Ser Ala Asp Leu Asp Lys
35 40 45

Cys Met Asp Cys Ala Ser Cys Arg Ala Arg Pro His Ser Asp Phe Cys
50 55 60

Leu Gly Cys Ala Ala Ala Pro Pro Ala Pro Phe Arg Leu Leu Trp Pro
65 70 75 80

Ile Leu Gly Gly Ala Leu Ser Leu Thr Phe Val Leu Gly Leu Leu Ser
85 90 95

Gly Phe Leu Val Trp Arg Arg Cys Arg Arg Arg Glu Lys Phe Thr Thr
100 105 110

Pro Ile Glu Glu Thr Gly Gly Glu Gly Cys Pro Ala Val Ala Leu Ile
115 120 125

Gln

<210> 437

<211> 247
<212> PRT
<213> Homo sapiens

<400> 437
Met Leu Arg Arg Arg Gly Ser Pro Gly Met Gly Val His Val Gly Ala
1 5 10 15

Ala Leu Gly Ala Leu Trp Phe Cys Leu Thr Gly Ala Leu Glu Val Gln
20 25 30

Val Pro Glu Asp Pro Val Val Ala Leu Val Gly Thr Asp Ala Thr Leu
35 40 45

Cys Cys Ser Phe Ser Pro Glu Pro Gly Phe Ser Leu Ala Gln Leu Asn
50 55 60

Leu Ile Trp Gln Leu Thr Asp Thr Lys Gln Leu Val His Ser Phe Ala
65 70 75 80

Glu Gly Gln Asp Gln Gly Ser Ala Tyr Ala Asn Arg Thr Ala Leu Phe
85 90 95

Leu Asp Leu Leu Ala Gln Gly Asn Ala Ser Leu Arg Leu Gln Arg Val
100 105 110

Arg Val Ala Asp Glu Gly Ser Phe Thr Cys Phe Val Ser Ile Arg Asp
115 120 125

Phe Gly Ser Ala Ala Val Ser Leu Gln Val Ala Ala Pro Tyr Ser Lys
130 135 140

Pro Ser Met Thr Leu Glu Pro Asn Lys Asp Leu Arg Pro Gly Asp Thr
145 150 155 160

Val Thr Ile Thr Cys Ser Ser Tyr Arg Gly Tyr Pro Glu Ala Glu Val
165 170 175

Phe Trp Gln Asp Gly Gln Gly Val Pro Leu Thr Gly Asn Val Thr Thr
180 185 190

Ser Gln Met Ala Asn Glu Gln Gly Leu Phe Asp Val His Ser Val Leu
195 200 205

Arg Val Val Leu Gly Ala Asn Gly Thr Tyr Ser Cys Leu Val Arg Asn
210 215 220

Pro Val Leu Gln Gln Asp Ala His Gly Ser Val Thr Ile Thr Gly Gln
225 230 235 240

Pro Met Thr Phe Pro Pro Glu
245

<210> 438
<211> 346
<212> PRT
<213> Homo sapiens

<400> 438

```
Met Ala Arg Pro Gly Gln Arg Trp Leu Gly Lys Trp Leu Val Ala Met
1               5                   10                  15

Val Val Trp Ala Leu Cys Arg Leu Ala Thr Pro Leu Ala Lys Asn Leu
            20                  25                  30

Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe Leu Ser Gly Lys
        35                  40                  45

Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu Asp Ile Ile Cys
    50                  55                  60

Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr Lys Leu Tyr Leu
65                  70                  75                  80

Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val Leu Asp Pro Asn
                85                  90                  95

Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile Arg Phe Thr Ile
            100                 105                 110

Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu Glu Phe Lys Lys
        115                 120                 125

His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly Ser Leu Glu Gly
    130                 135                 140

Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg Thr Met Lys Ile
145                 150                 155                 160

Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr Pro Glu Gln Leu
                165                 170                 175

Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr Val Lys Met Ala
            180                 185                 190

Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp Ser Asp Gly Lys
        195                 200                 205

His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro Gly Ala Ser Gly
    210                 215                 220

Gly Ser Ser Gly Asp Pro Asp Gly Phe Phe Asn Ser Lys Val Ala Leu
225                 230                 235                 240

Phe Ala Ala Val Gly Ala Gly Cys Val Ile Phe Leu Leu Ile Ile Ile
                245                 250                 255

Phe Leu Thr Val Leu Leu Leu Lys Leu Arg Lys Arg His Arg Lys His
            260                 265                 270

Thr Gln Gln Arg Ala Ala Ala Leu Ser Leu Ser Thr Leu Ala Ser Pro
        275                 280                 285

Lys Gly Gly Ser Gly Thr Ala Gly Thr Glu Pro Ser Asp Ile Ile Ile
    290                 295                 300

Pro Leu Arg Thr Thr Glu Asn Asn Tyr Cys Pro His Tyr Glu Lys Val
305                 310                 315                 320

Ser Gly Asp Tyr Gly His Pro Val Tyr Ile Val Gln Glu Met Pro Pro
```

325 330 335

Gln Ser Pro Ala Asn Ile Tyr Tyr Lys Val
340 345

<210> 439
<211> 346
<212> PRT
<213> Homo sapiens

<400> 439
Met Ala Arg Pro Gly Gln Arg Trp Leu Gly Lys Trp Leu Val Ala Met
1 5 10 15

Val Val Trp Ala Leu Cys Arg Leu Ala Thr Pro Leu Ala Lys Asn Leu
20 25 30

Glu Pro Val Ser Trp Ser Ser Leu Asn Pro Lys Phe Leu Ser Gly Lys
35 40 45

Gly Leu Val Ile Tyr Pro Lys Ile Gly Asp Lys Leu Asp Ile Ile Cys
50 55 60

Pro Arg Ala Glu Ala Gly Arg Pro Tyr Glu Tyr Tyr Lys Leu Tyr Leu
65 70 75 80

Val Arg Pro Glu Gln Ala Ala Ala Cys Ser Thr Val Leu Asp Pro Asn
85 90 95

Val Leu Val Thr Cys Asn Arg Pro Glu Gln Glu Ile Arg Phe Thr Ile
100 105 110

Lys Phe Gln Glu Phe Ser Pro Asn Tyr Met Gly Leu Glu Phe Lys Lys
115 120 125

His His Asp Tyr Tyr Ile Thr Ser Thr Ser Asn Gly Ser Leu Glu Gly
130 135 140

Leu Glu Asn Arg Glu Gly Gly Val Cys Arg Thr Arg Thr Met Lys Ile
145 150 155 160

Ile Met Lys Val Gly Gln Asp Pro Asn Ala Val Thr Pro Glu Gln Leu
165 170 175

Thr Thr Ser Arg Pro Ser Lys Glu Ala Asp Asn Thr Val Lys Met Ala
180 185 190

Thr Gln Ala Pro Gly Ser Arg Gly Ser Leu Gly Asp Ser Asp Gly Lys
195 200 205

His Glu Thr Val Asn Gln Glu Glu Lys Ser Gly Pro Gly Ala Ser Gly
210 215 220

Gly Ser Ser Gly Asp Pro Asp Gly Phe Phe Asn Ser Lys Val Ala Leu
225 230 235 240

Phe Ala Ala Val Gly Ala Gly Cys Val Ile Phe Leu Leu Ile Ile Ile
245 250 255

Phe Leu Thr Val Leu Leu Leu Lys Leu Arg Lys Arg His Arg Lys His
260 265 270

Thr Gln Gln Arg Ala Ala Ala Leu Ser Leu Ser Thr Leu Ala Ser Pro
275 280 285

Lys Gly Gly Ser Gly Thr Ala Gly Thr Glu Pro Ser Asp Ile Ile Ile
290 295 300

Pro Leu Arg Thr Thr Glu Asn Asn Tyr Cys Pro His Tyr Glu Lys Val
305 310 315 320

Ser Gly Asp Tyr Gly His Pro Val Tyr Ile Val Gln Glu Met Pro Pro
325 330 335

Gln Ser Pro Ala Asn Ile Tyr Tyr Lys Val
340 345

<210> 440
<211> 319
<212> PRT
<213> Pan troglodytes

<220>
<221> MUTAGEN
<222> (30)
<223> Natural stop codon replaced by Arg

<400> 440
Met Pro Val Phe Ser Leu Gln Asn Asp Glu Val Glu Phe Val Arg Thr
1 5 10 15

Gly Tyr Gly Lys Asp Ile Val Lys Val Leu His Ile Gln Arg Asp Gly
20 25 30

Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln Leu Thr Leu
35 40 45

Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp Ile Ile Pro
50 55 60

Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys Phe Lys Glu
65 70 75 80

Asn Glu Pro Ala Asn Ile Asp Gly Ala Met Glu Lys Ala Phe Cys Phe
85 90 95

Phe Leu Gln Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu
100 105 110

His Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr Val
115 120 125

Glu Glu Ile Pro Trp Lys His Leu Glu Lys Asn Gly Val Lys His Val
130 135 140

His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Gly Glu Val Glu
145 150 155 160

```
Gln Leu Arg Ser Gly Pro Gln Val Ile His Ser Gly Ile Lys Asp Leu
                165                 170                 175

Lys Leu Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
            180                 185                 190

Gln Phe Thr Thr Leu Pro Glu Val Phe Lys Cys Met Met Arg Thr Leu
        195                 200                 205

Pro Gln Ser Ser Phe Pro Leu Phe Gln Val Leu Ser Met Gly Ser Ser
    210                 215                 220

Leu Met Asp Thr Ile Arg Asp Leu Val Met Glu Lys Ser Ala Gly Pro
225                 230                 235                 240

Tyr Asp Lys Asp Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Cys Asp
                245                 250                 255

Ile Gln Val Leu Ser Leu Ser Arg Val Pro Ala Ile Glu Asp Met Glu
            260                 265                 270

Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met
        275                 280                 285

Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr
    290                 295                 300

Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
305                 310                 315


<210> 441
<211> 319
<212> PRT
<213> Pan troglodytes

<220>
<221> MUTAGEN
<222> (30)
<223> Natural stop codon replaced by Arg

<400> 441
Met Pro Val Phe Ser Leu Gln Asn Asp Glu Val Glu Phe Val Arg Thr
1               5                   10                  15

Gly Tyr Gly Lys Asp Ile Val Lys Val Leu His Ile Gln Arg Asp Gly
            20                  25                  30

Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln Leu Thr Leu
        35                  40                  45

Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp Ile Ile Pro
    50                  55                  60

Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys Phe Lys Glu
65                  70                  75                  80

Asn Glu Pro Ala Asn Ile Asp Gly Ala Met Glu Lys Ala Phe Cys Phe
                85                  90                  95
```

```
Phe Leu Gln Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu
            100                 105                 110

His Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr Val
        115                 120                 125

Glu Glu Ile Pro Trp Lys His Leu Glu Lys Asn Gly Val Lys His Val
    130                 135                 140

His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Gly Glu Val Glu
145                 150                 155                 160

Gln Leu Arg Ser Gly Pro Gln Val Ile His Ser Gly Ile Lys Asp Leu
                165                 170                 175

Lys Leu Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
            180                 185                 190

Gln Phe Thr Thr Leu Pro Glu Val Phe Lys Cys Met Met Arg Thr Leu
        195                 200                 205

Pro Gln Ser Ser Phe Pro Leu Phe Gln Val Leu Ser Met Gly Ser Ser
    210                 215                 220

Leu Met Asp Thr Ile Arg Asp Leu Val Met Glu Lys Ser Ala Gly Pro
225                 230                 235                 240

Tyr Asp Lys Asp Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Cys Asp
                245                 250                 255

Ile Gln Val Leu Ser Leu Ser Arg Val Pro Ala Ile Glu Asp Met Glu
            260                 265                 270

Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met
        275                 280                 285

Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr
    290                 295                 300

Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
305                 310                 315
```

<210> 442
<211> 394
<212> PRT
<213> Homo sapiens

<220>
<221> MUTAGEN
<222> (104)
<223> Natural stop codon replaced by Arg

<220>
<221> MUTAGEN
<222> (277)
<223> Natural stop codon replaced by Arg

<400> 442
Met Glu Lys Phe Ile Trp Tyr Leu Val His Leu Tyr Thr Glu Met Thr

1 5 10 15

Lys Ser Ser Pro Ser Cys Arg Leu Val Ala Ser Cys Gln Thr Val Ala
20 25 30

Lys Glu Leu Gly Glu Asn Ser Leu Gly Tyr Gly Pro Gly His Tyr Leu
35 40 45

Leu Phe Gly Cys Arg Asp Ala Phe Gly Cys Pro Met Pro Gly Leu Phe
50 55 60

His Leu Leu Gln Asp Gln Met Ile Gly Ser Leu His Thr Asp Ser Leu
65 70 75 80

Pro Asn Asp Glu Val Glu Phe Val Arg Thr Gly Tyr Gly Lys Glu Met
85 90 95

Val Lys Val Leu His Ile Gln Arg Asp Gly Lys Tyr His Ser Ile Lys
100 105 110

Glu Val Ala Thr Ser Val Gln Leu Thr Leu Ser Ser Lys Lys Asp Tyr
115 120 125

Leu His Gly Asp Asn Ser Asp Ile Ile Pro Thr Asp Thr Ile Lys Asn
130 135 140

Thr Val His Val Leu Ala Lys Phe Lys Glu Asn Asp Pro Ala Asn Ile
145 150 155 160

Asp Gly Ala Met Glu Lys Ala Phe Cys Phe Phe Leu Gln Ile Lys Ser
165 170 175

Ile Glu Ala Phe Gly Val Asn Ile Cys Glu His Phe Leu Ser Ser Phe
180 185 190

Asn His Val Ile Arg Ala Gln Val Tyr Met Glu Glu Ile Pro Trp Lys
195 200 205

His Leu Gly Lys Asn Gly Val Lys His Val His Ala Phe Ile His Thr
210 215 220

Pro Thr Gly Thr His Phe Cys Glu Val Glu Gln Leu Arg Ser Gly Pro
225 230 235 240

Gln Val Ile His Ser Gly Ile Lys Asp Leu Lys Val Leu Lys Thr Thr
245 250 255

Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp Gln Phe Thr Thr Leu Pro
260 265 270

Glu Val Lys Asp Arg Cys Phe Ala Thr Gln Val Tyr Cys Lys Trp Arg
275 280 285

Tyr His Gln Cys Arg Asp Val Asp Phe Lys Ala Thr Trp Asp Thr Ile
290 295 300

Arg Asp Leu Val Met Glu Lys Ser Ala Gly Pro Tyr Asp Lys Gly Glu
305 310 315 320

Tyr Leu Thr Ser Val Gln Lys Thr Leu Cys Asp Ile Gln Val Leu Ser
325 330 335

Leu Ser Arg Val Pro Ala Ile Glu Asp Met Glu Ile Ser Leu Pro Asn
340 345 350

Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met Gly Leu Ile Asn Lys
355 360 365

Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr Gly Lys Ile Thr Gly
370 375 380

Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
385 390

<210> 443
<211> 394
<212> PRT
<213> Homo sapiens

<220>
<221> MUTAGEN
<222> (104)
<223> Natural stop codon replaced by Arg

<220>
<221> MUTAGEN
<222> (277)
<223> Natural stop codon replaced by Arg

<400> 443
Met Glu Lys Phe Ile Trp Tyr Leu Val His Leu Tyr Thr Glu Met Thr
1 5 10 15

Lys Ser Ser Pro Ser Cys Arg Leu Val Ala Ser Cys Gln Thr Val Ala
20 25 30

Lys Glu Leu Gly Glu Asn Ser Leu Gly Tyr Gly Pro Gly His Tyr Leu
35 40 45

Leu Phe Gly Cys Arg Asp Ala Phe Gly Cys Pro Met Pro Gly Leu Phe
50 55 60

His Leu Leu Gln Asp Gln Met Ile Gly Ser Leu His Thr Asp Ser Leu
65 70 75 80

Pro Asn Asp Glu Val Glu Phe Val Arg Thr Gly Tyr Gly Lys Glu Met
85 90 95

Val Lys Val Leu His Ile Gln Arg Asp Gly Lys Tyr His Ser Ile Lys
100 105 110

Glu Val Ala Thr Ser Val Gln Leu Thr Leu Ser Ser Lys Lys Asp Tyr
115 120 125

Leu His Gly Asp Asn Ser Asp Ile Ile Pro Thr Asp Thr Ile Lys Asn
130 135 140

Thr Val His Val Leu Ala Lys Phe Lys Glu Asn Asp Pro Ala Asn Ile
145 150 155 160

Asp Gly Ala Met Glu Lys Ala Phe Cys Phe Phe Leu Gln Ile Lys Ser
165 170 175

Ile Glu Ala Phe Gly Val Asn Ile Cys Glu His Phe Leu Ser Ser Phe
180 185 190

Asn His Val Ile Arg Ala Gln Val Tyr Met Glu Glu Ile Pro Trp Lys
195 200 205

His Leu Gly Lys Asn Gly Val Lys His Val His Ala Phe Ile His Thr
210 215 220

Pro Thr Gly Thr His Phe Cys Glu Val Glu Gln Leu Arg Ser Gly Pro
225 230 235 240

Gln Val Ile His Ser Gly Ile Lys Asp Leu Lys Val Leu Lys Thr Thr
245 250 255

Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp Gln Phe Thr Thr Leu Pro
260 265 270

Glu Val Lys Asp Arg Cys Phe Ala Thr Gln Val Tyr Cys Lys Trp Arg
275 280 285

Tyr His Gln Cys Arg Asp Val Asp Phe Lys Ala Thr Trp Asp Thr Ile
290 295 300

Arg Asp Leu Val Met Glu Lys Ser Ala Gly Pro Tyr Asp Lys Gly Glu
305 310 315 320

Tyr Leu Thr Ser Val Gln Lys Thr Leu Cys Asp Ile Gln Val Leu Ser
325 330 335

Leu Ser Arg Val Pro Ala Ile Glu Asp Met Glu Ile Ser Leu Pro Asn
340 345 350

Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met Gly Leu Ile Asn Lys
355 360 365

Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr Gly Lys Ile Thr Gly
370 375 380

Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
385 390

<210> 444
<211> 304
<212> PRT
<213> Papio hamadryas

<400> 444
Met Ala Asp Tyr His Asn Asn Tyr Lys Lys Asn Asp Glu Leu Glu Phe
1 5 10 15

Val Arg Thr Gly Tyr Gly Lys Asp Met Val Lys Val Leu His Ile Gln
20 25 30

Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
35 40 45

Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
50 55 60

Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys
65 70 75 80

Phe Lys Gly Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu
85 90 95

Tyr Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr Val
100 105 110

Glu Glu Ile Pro Trp Lys Arg Leu Glu Lys Asn Gly Val Lys His Val
115 120 125

His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu
130 135 140

Gln Leu Arg Ser Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp Leu
145 150 155 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
165 170 175

Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
180 185 190

Val Tyr Cys Lys Trp Arg Tyr His Gln Cys Arg Asp Val Asp Phe Glu
195 200 205

Ala Thr Trp Gly Thr Ile Arg Asp Leu Val Leu Glu Lys Phe Ala Gly
210 215 220

Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
225 230 235 240

Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro Glu Ile Glu Asp Met
245 250 255

Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys
260 265 270

Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro
275 280 285

Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
290 295 300

<210> 445
<211> 304
<212> PRT
<213> Papio hamadryas

<400> 445
Met Ala Asp Tyr His Asn Asn Tyr Lys Lys Asn Asp Glu Leu Glu Phe
1 5 10 15

Val Arg Thr Gly Tyr Gly Lys Asp Met Val Lys Val Leu His Ile Gln
20 25 30

```
Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
        35                  40                  45

Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
    50                  55                  60

Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys
65                  70                  75                  80

Phe Lys Gly Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu
                85                  90                  95

Tyr Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr Val
            100                 105                 110

Glu Glu Ile Pro Trp Lys Arg Leu Glu Lys Asn Gly Val Lys His Val
        115                 120                 125

His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu
    130                 135                 140

Gln Leu Arg Ser Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp Leu
145                 150                 155                 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
                165                 170                 175

Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
            180                 185                 190

Val Tyr Cys Lys Trp Arg Tyr His Gln Cys Arg Asp Val Asp Phe Glu
        195                 200                 205

Ala Thr Trp Gly Thr Ile Arg Asp Leu Val Leu Glu Lys Phe Ala Gly
    210                 215                 220

Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
225                 230                 235                 240

Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro Glu Ile Glu Asp Met
                245                 250                 255

Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys
            260                 265                 270

Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro
        275                 280                 285

Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
    290                 295                 300
```

<210> 446
<211> 394
<212> PRT
<213> Homo sapiens

<220>
<221> MUTAGEN
<222> (104)
<223> Natural stop codon replaced by Arg

<220>
<221> MUTAGEN
<222> (277)
<223> Natural stop codon replaced by Arg

<400> 446
Met Glu Lys Phe Ile Trp Tyr Leu Val His Leu Tyr Thr Glu Met Thr
1 5 10 15

Lys Ser Ser Pro Ser Cys Arg Leu Val Ala Ser Cys Gln Thr Val Ala
20 25 30

Lys Glu Leu Gly Glu Asn Ser Leu Gly Tyr Gly Pro Gly His Tyr Leu
35 40 45

Leu Phe Gly Cys Arg Asp Ala Phe Gly Cys Pro Met Pro Gly Leu Phe
50 55 60

His Leu Leu Gln Asp Gln Met Ile Gly Ser Leu His Thr Asp Ser Leu
65 70 75 80

Pro Asn Asp Glu Val Glu Phe Val Arg Thr Gly Tyr Gly Lys Glu Met
85 90 95

Val Lys Val Leu His Ile Gln Arg Asp Gly Lys Tyr His Ser Ile Lys
100 105 110

Glu Val Ala Thr Ser Val Gln Leu Thr Leu Ser Ser Lys Lys Asp Tyr
115 120 125

Leu His Gly Asp Asn Ser Asp Ile Ile Pro Thr Asp Thr Ile Lys Asn
130 135 140

Thr Val His Val Leu Ala Lys Phe Lys Glu Asn Asp Pro Ala Asn Ile
145 150 155 160

Asp Gly Ala Met Glu Lys Ala Phe Cys Phe Phe Leu Gln Ile Lys Ser
165 170 175

Ile Glu Ala Phe Gly Val Asn Ile Cys Glu His Phe Leu Ser Ser Phe
180 185 190

Asn His Val Ile Arg Ala Gln Val Tyr Met Glu Glu Ile Pro Trp Lys
195 200 205

His Leu Gly Lys Asn Gly Val Lys His Val His Ala Phe Ile His Thr
210 215 220

Pro Thr Gly Thr His Phe Cys Glu Val Glu Gln Leu Arg Ser Gly Pro
225 230 235 240

Gln Val Ile His Ser Gly Ile Lys Asp Leu Lys Val Leu Lys Thr Thr
245 250 255

Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp Gln Phe Thr Thr Leu Pro
260 265 270

Glu Val Lys Asp Arg Cys Phe Ala Thr Gln Val Tyr Cys Lys Trp Arg
275 280 285

Tyr His Gln Cys Arg Asp Val Asp Phe Lys Ala Thr Trp Asp Thr Ile
290 295 300

Arg Asp Leu Val Met Glu Lys Ser Ala Gly Pro Tyr Asp Lys Gly Glu
305 310 315 320

Tyr Leu Thr Ser Val Gln Lys Thr Leu Cys Asp Ile Gln Val Leu Ser
325 330 335

Leu Ser Arg Val Pro Ala Ile Glu Asp Met Glu Ile Ser Leu Pro Asn
340 345 350

Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met Gly Leu Ile Asn Lys
355 360 365

Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr Gly Lys Ile Thr Gly
370 375 380

Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
385 390

<210> 447
<211> 319
<212> PRT
<213> Pan troglodytes

<220>
<221> MUTAGEN
<222> (30)
<223> Natural stop codon replaced by Arg

<400> 447
Met Pro Val Phe Ser Leu Gln Asn Asp Glu Val Glu Phe Val Arg Thr
1 5 10 15

Gly Tyr Gly Lys Asp Ile Val Lys Val Leu His Ile Gln Arg Asp Gly
20 25 30

Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln Leu Thr Leu
35 40 45

Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp Ile Ile Pro
50 55 60

Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys Phe Lys Glu
65 70 75 80

Asn Glu Pro Ala Asn Ile Asp Gly Ala Met Glu Lys Ala Phe Cys Phe
85 90 95

Phe Leu Gln Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu
100 105 110

His Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr Val
115 120 125

Glu Glu Ile Pro Trp Lys His Leu Glu Lys Asn Gly Val Lys His Val
130 135 140

```
His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Gly Glu Val Glu
145                 150                 155                 160

Gln Leu Arg Ser Gly Pro Gln Val Ile His Ser Gly Ile Lys Asp Leu
                165                 170                 175

Lys Leu Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
            180                 185                 190

Gln Phe Thr Thr Leu Pro Glu Val Phe Lys Cys Met Met Arg Thr Leu
        195                 200                 205

Pro Gln Ser Ser Phe Pro Leu Phe Gln Val Leu Ser Met Gly Ser Ser
    210                 215                 220

Leu Met Asp Thr Ile Arg Asp Leu Val Met Glu Lys Ser Ala Gly Pro
225                 230                 235                 240

Tyr Asp Lys Asp Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Cys Asp
                245                 250                 255

Ile Gln Val Leu Ser Leu Ser Arg Val Pro Ala Ile Glu Asp Met Glu
            260                 265                 270

Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys Met
        275                 280                 285

Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro Tyr
    290                 295                 300

Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
305                 310                 315


<210> 448
<211> 304
<212> PRT
<213> Papio hamadryas

<400> 448
Met Ala Asp Tyr His Asn Asn Tyr Lys Lys Asn Asp Glu Leu Glu Phe
 1               5                  10                  15

Val Arg Thr Gly Tyr Gly Lys Asp Met Val Lys Val Leu His Ile Gln
            20                  25                  30

Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
        35                  40                  45

Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
    50                  55                  60

Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys
65                  70                  75                  80

Phe Lys Gly Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu
                85                  90                  95

Tyr Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr Val
            100                 105                 110
```

```
Glu Glu Ile Pro Trp Lys Arg Leu Glu Lys Asn Gly Val Lys His Val
        115                 120                 125

His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu
    130                 135                 140

Gln Leu Arg Ser Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp Leu
145                 150                 155                 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
                165                 170                 175

Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
            180                 185                 190

Val Tyr Cys Lys Trp Arg Tyr His Gln Cys Arg Asp Val Asp Phe Glu
        195                 200                 205

Ala Thr Trp Gly Thr Ile Arg Asp Leu Val Leu Glu Lys Phe Ala Gly
    210                 215                 220

Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
225                 230                 235                 240

Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro Glu Ile Glu Asp Met
                245                 250                 255

Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys
            260                 265                 270

Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro
        275                 280                 285

Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
    290                 295                 300
```

<210> 449
<211> 23
<212> DNA
<213> Homo sapiens

<400> 449
caccaaatgc tgcacagaat cct 23

<210> 450
<211> 20
<212> DNA
<213> Homo sapiens

<400> 450
acctgaccta caggaaagag 20

<210> 451
<211> 23
<212> DNA
<213> Homo sapiens

<400> 451
caccaaatgc tgcacagaat cct 23

<210> 452
<211> 20
<212> DNA
<213> Homo sapiens

<400> 452
acctgaccta caggaaagag 20

<210> 453
<211> 23
<212> DNA
<213> Homo sapiens

<400> 453
caccaaatgc tgcacagaat cct 23

<210> 454
<211> 20
<212> DNA
<213> Homo sapiens

<400> 454
acctgaccta caggaaagag 20

<210> 455
<211> 20
<212> DNA
<213> Homo sapiens

<400> 455
catacaaact taagagtcca 20

<210> 456
<211> 67
<212> DNA
<213> Homo sapiens

<400> 456
ctttaaatcg atgagcaacc tcactcttgt gtgcatctct cttatccaaa gaaccggaat 60
aagccga 67

<210> 457
<211> 20
<212> DNA
<213> Homo sapiens

<400> 457
catacaaact taagagtcca 20

<210> 458
<211> 67
<212> DNA
<213> Homo sapiens

<400> 458
ctttaaatcg atgagcaacc tcactcttgt gtgcatctct cttatccaaa gaaccggaat 60
aagccga 67

<210> 459
<211> 27
<212> DNA
<213> Homo sapiens

<400> 459
gttagcagag tagcagggct ttcggct 27

<210> 460
<211> 95
<212> DNA
<213> Homo sapiens

<400> 460
caagcaatga attccttagc agcttgacct tccaagtaag aagaaacatc agaagtgaaa 60
gtaccttcac cgtgtctctt atccaaagaa ccgga 95

<210> 461
<211> 103
<212> DNA
<213> Homo sapiens

<400> 461
gagcgcaagc ttccgccatc atgaaggtct ccgtggctgc cctctcctgc ctcatgcttg 60
ttactgccct tggatcccag gccagcccca agatggtgca agg 103

<210> 462
<211> 57
<212> DNA
<213> Homo sapiens

<400> 462
agtcccatcg atgagcaacc tcactcttgt gtgcatcatg ccgcctcagc actttgc 57

<210> 463
<211> 103
<212> DNA
<213> Homo sapiens

<400> 463
gagcgcaagc ttccgccatc atgtggtggc gcctgtggtg gctgctgctg ctgctgctgc 60
tgctgtggcc catggtgtgg gccagcccca agatggtgca agg 103

<210> 464
<211> 57
<212> DNA
<213> Homo sapiens

<400> 464
agtcccatcg atgagcaacc tcactcttgt gtgcatcatg ccgcctcagc actttgc 57

<210> 465
<211> 104
<212> DNA
<213> Homo sapiens

<400> 465
tcccccgggg ccgccaccat gaaggtctcc gtggctgccc tctcctgcct catgcttgtt 60
actgcccttg gatcccaggc ccacggtgaa ggtactttca cttc 104

<210> 466

<211> 49
<212> DNA
<213> Homo sapiens

<400> 466
cgattgatca ttattataag cctaaggcag cttgacttgc agcaacaag 49

<210> 467
<211> 38
<212> DNA
<213> Homo sapiens

<400> 467
aggagcgtcg acaaaagaag ccccaagatg gtgcaagg 38

<210> 468
<211> 26
<212> DNA
<213> Homo sapiens

<400> 468
ttataagcct aaggcagctt gacttg 26

<210> 469
<211> 115
<212> DNA
<213> Homo sapiens

<400> 469
gagcgcggat ccaagcttcc gccatcatgc gccccacctg ggcctggtgg ctgttcctgg 60
tgctgctgct ggccctgtgg gcccccgccc gcggcagccc caagatggtg caagg 115

<210> 470
<211> 57
<212> DNA
<213> Homo sapiens

<400> 470
agtcccatcg atgagcaacc tcactcttgt gtgcatcatg ccgcctcagc actttgc 57

<210> 471
<211> 29
<212> DNA
<213> Homo sapiens

<400> 471
gagcgcggat ccaagcttcc gccatcatg 29

<210> 472
<211> 26
<212> DNA
<213> Homo sapiens

<400> 472
ctttaaatcg atgagcaacc tcactc 26

<210> 473
<211> 109
<212> DNA
<213> Homo sapiens

<400> 473
gagcgcggat ccaagcttcc gccatcatgt ggtggcgcct gtggtggctg ctgctgctgc 60
tgctgctgct gtggcccatg gtgtgggcca gccccaagat ggtgcaagg 109

<210> 474
<211> 38
<212> DNA
<213> Homo sapiens

<400> 474
gtcgtcggta ccttataagc ctaaggcagc ttgacttg 38

<210> 475
<211> 80
<212> DNA
<213> Homo sapiens

<400> 475
gagcgcggat ccaagcttcc gccatcatgt ggtggcgcct gtggtggctg ctgctgctgc 60
tgctgctgct gtggcccatg 80

<210> 476
<211> 57
<212> DNA
<213> Homo sapiens

<400> 476
agtcccatcg atgagcaacc tcactcttgt gtgcatcatg ccgcctcagc actttgc 57

<210> 477
<211> 80
<212> DNA
<213> Homo sapiens

<400> 477
gagcgcggat ccaagcttcc gccatcatgt ggtggcgcct gtggtggctg ctgctgctgc 60
tgctgctgct gtggcccatg 80

<210> 478
<211> 57
<212> DNA
<213> Homo sapiens

<400> 478
agtcccatcg atgagcaacc tcactcttgt gtgcatcatg ccgcctcagc actttgc 57

<210> 479
<211> 80
<212> DNA
<213> Homo sapiens

<400> 479
aagctgcctt aggcttaagc cccaagatgg tgcaagggtc tggctgcttt gggaggaaga 60
tggaccggat cagctcctcc 80

<210> 480
<211> 64
<212> DNA
<213> Homo sapiens

<400> 480

gcaccgggcg cgccttaatg ccgcctcagc actttgcagc ccaggccact ggaggagctg 60
atcc 64

<210> 481
<211> 37
<212> DNA
<213> Homo sapiens

<400> 481
aggagcgtcg acaaaagaag ccccaagatg gtgcaag 37

<210> 482
<211> 56
<212> DNA
<213> Homo sapiens

<400> 482
cgcgcatcga tgagcaacct cactcttgtg tgcatcatgc cgcctcagca ctttgc 56

<210> 483
<211> 670
<212> PRT
<213> Homo sapiens

<400> 483
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
50 55 60

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
65 70 75 80

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
85 90 95

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
100 105 110

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
115 120 125

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
130 135 140

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
145 150 155 160

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
165 170 175

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
180 185 190

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
    195   200   205

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
    210   215   220

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
225   230   235   240

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
                245   250   255

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
            260   265   270

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
        275   280   285

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
    290   295   300

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
305   310   315   320

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
                325   330   335

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
            340   345   350

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
        355   360   365

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
    370   375   380

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
385   390   395   400

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
                405   410   415

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
            420   425   430

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
        435   440   445

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
    450   455   460

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
465   470   475   480

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
                485   490   495

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
            500   505   510

```
Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
            515                 520                 525

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
    530                 535                 540

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
545                 550                 555                 560

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
                565                 570                 575

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
            580                 585                 590

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
        595                 600                 605

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
    610                 615                 620

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
625                 630                 635                 640

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
                645                 650                 655

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665                 670
```

<210> 484
<211> 96
<212> DNA
<213> Homo sapiens

<400> 484

```
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc      60
tccagtggcc tgggctgcaa agtgctgagg cggcat                                96
```

<210> 485
<211> 32
<212> PRT
<213> Homo sapiens

<400> 485

```
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1               5                   10                  15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
            20                  25                  30
```

<210> 486
<211> 95
<212> DNA
<213> Homo sapiens

<400> 486

```
agccccaaga tggtgcaagg gtctggctgc tttgggagga agatggaccg gatcagctcc      60
```

tccagtggct gggctgcaaa gtgctgaggc ggcat 95

<210> 487
<211> 40
<212> DNA
<213> Homo sapiens

<400> 487
ccttgcacca tcttggggct atgccgcctc agcactttgc 40

<210> 488
<211> 40
<212> DNA
<213> Homo sapiens

<400> 488
gcaaagtgct gaggcggcat agccccaaga tggtgcaagg 40

<210> 489
<211> 57
<212> DNA
<213> Homo sapiens

<400> 489
agtcccatcg atgagcaacc tcactcttgt gtgcatcatg ccgcctcagc actttgc 57